

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207026Orig1s000

CHEMISTRY REVIEW(S)



CMC Memo to File

To:	NDA
Date	18 Dec 2014
Drug:	Phoxillium Replacement Solution
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “approve” recommendation given on 15-Dec-2014 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 202-270 be approved. A re-evaluation date of (b) (4) has been issued for the application’s facilities. There are no pending CMC review deficiencies.

Overall Manufacturing Inspection Recommendation [Next task >](#)

NDA 207026-Orig1-New/NDA(1)

Task Details Task Data Open Issues More ▾

Overview

Task Instructions	Assigned To	Pln Comp	Status	Actions
No Description	Vibhakar Shah	5/26/14	Complete	

1 Result

Vibhakar Shah (b) (4) updated Facility Inspection - Overall Application Recommendation to Approve and updated Facility Inspection - Overall Application Re-evaluation Date to
10 hours ago - Comment

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.12.19 09:18:44 -05'00'

Olen Stephens, Ph.D.
Acting Branch I Chief, ONDQA

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
- 2. NDA Number: 207026
 - Submission Date: 03/13/2014
 - 21st C. Review Goal Date: 12/09/2014
 - PDUFA Goal Date: 01/13/2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Phoxilium BK 4/2.5 and B22K 4/0
Established or Non-Proprietary Name (USAN) and strength:	-
Dosage Form:	Sterile Solution

4. SUBMISSION PROPERTIES:

Review Priority :	Original STANDARD
Applicant Name:	Gambro Lundia AB
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

II. Application Detail

1. INDICATION: Replacement solution in patients undergoing Continuous Renal Replacement Therapy (CRRT)
2. ROUTE OF ADMINISTRATION: In the extracorporeal circuit for CRRT
3. STRENGTH/POTENCY: BK4/2.5 and B22K4/0 (as shown below)

(in mEq/L except where noted)	Phoxilium BK4/2.5	Phoxilium B22K4/0
Calcium Ca ²⁺	2.5	0
Magnesium Mg ²⁺	1.5	1.5
Sodium Na ⁺	140	140
Chloride Cl ⁻	114.5	122.0
Bicarbonate HCO ₃ ⁻	32	22
Potassium K ⁺	4.0	4.0
Phosphate HPO ₄ ²⁻	1 mmol/L	1 mmol/L
Theoretical Osmolarity	294 mOsm/L	290 mOsm/L

4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		505(b)(2)
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue)			
	1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		1 st FDA evaluation for one of the establishments: (b) (4) (FEI: (b) (4))
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	X		
	Have all EERs been updated with final PAI recommendation?		X	
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights:

1. Drug Substance

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	All drug substances are USP grade compounds, generally used as electrolytes, except for NaHCO ₃ . The electrolytes, calcium, magnesium, chloride, potassium sodium and phosphate are normal plasma constituents and Bicarbonate is used as a basic buffer to combat acidosis

Drug Substance Manufacturing Process flow chart/diagram (see eCTD Section 3.2.S.2.2)

The flow diagrams for the synthesis/manufacture of all the **drug substances** are reproduced from the NDA in **figures 1a-1h** on **pages 6-11** of this report.

2. Drug Product

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Drug Product Manufacturing Process flow chart/diagram (see eCTD Section 3.2.P.3.3)

The drug product, Phoxillium Sterile Solution, is manufactured by Gambro, (b) (4) and the flow chart of the manufacturing process is reproduced from the NDA in **Figure 2** on **page 12** of this report.

3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.): None

Additional information on Manufacturing issues or Complexities

Drug Substance: None

Drug Product: None

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Drug substance and Drug Product Manufacturing Facilities Chart

(generated from 602A DARRTS report and OMPQ macro)

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Facts Assignment ID	Inspection Start-End Dates	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b) (4)						(b) (4)	-	-	OC Recommendation	AC	EER ReEval: (b) (4)
						(b) (4)	-	-	OC Recommendation	AC	(b) (4)
						(b) (4)	-	-	OC Recommendation	AC	
						(b) (4)	(b) (4)	TBD	Assigned Inspection to IB	PN	
						(b) (4)	-	-	OC Recommendation	AC	EER ReEval: (b) (4)
Gambro Renal Products	1051129	FLA	USA	Manufacture and release and stability testing of the Drug product	LVP	(b) (4) [AC, 08/15/2013]	-	-	OC Recommendation	AC	EER ReEval: (b) (4)

AC: Acceptable; NA: Not Applicable; TBD: To be determined; PN; Pending

Chart Status update: 05/27/2014

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no)	YES
At this time, is a KTM warranted for any PAI? (yes – site / no):	NO
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):	NO
Comments for 74 Day Letter	None
1.	
2.	
3.	

REVIEW AND APPROVAL

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

/s/

VIBHAKAR J SHAH
11/26/2014

MAHESH R RAMANADHAM
11/26/2014



NDA 207026

Phoxilium Replacement Solution

Gambro Renal Products

Sherita D. McLamore-Hines, Ph.D.

Division of Pre-Marketing Assessment 1
Office of Drug Quality Assessment



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Chemistry Review Data Sheet

1. NDA 207026
2. REVIEW #1
3. REVIEW DATE: November 12, 2014
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

n/a

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission
Amendment

Document Date

March 13, 2014
April 23, 2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Gambro Lundia AB
Address:	PO Box 10101 Lund Sweden SE-220 10
US Agent:	1845 Mason Avenue Daytona Beach, FL 32117 386-274-2811



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Phoxilium
- b) Non-Proprietary Name (USAN): n/a
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Continuous Renal Replacement Therapy

11. DOSAGE FORM: Sterile Solution

12. STRENGTH/POTENCY:

(in mEq/L except where noted)	Phoxilium BK4/2.5	Phoxilium B22K4/0
Sodium Na ⁺	140	140
Potassium K ⁺	4.0	4.0
Calcium Ca ²⁺	2.5	0
Magnesium Mg ²⁺	1.5	1.5
Chloride Cl ⁻	114.5	122.0
Phosphate HPO ₄ ²⁻	1 mmol/L	1 mmol/L
Bicarbonate HCO ₃ ⁻	32	22
Theoretical Osmolarity	(b) (4) mOsm/L	290 mOsm/L

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemical Names: Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Diabasic Sodium Phosphate and Sodium Bicarbonate

Molecular Weights: 58.4425, 74.551, 147.015, 203.302, (b)(4) and 84.0066

Molecular Formula: NaCl, KCl, CaCl₂·2H₂O, MgCl₂·6H₂O, Na₂HPO₄·2H₂O, NaHCO₃

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	II		(b)(4)	1	Adequate	August 5, 2014	
	II		1	Adequate	August 15, 2014		
	II		1	Adequate	August 5, 2014		
	II		3	Adequate	July 12, 2012		
	II		1	Adequate	August 13, 2014		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-703	Comparative electrolyte solution

18. STATUS:

ONDC:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	
Pharm/Tox	N/A	N/A	N/A
Biopharm	Approval	N/A	Okpo Eradiri
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore- Hines,
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	7/21/2014	Sherita McLamore-Hines,
Microbiology	Pending	Pending	Denise Miller

Chemistry Review for NDA 207026

Executive Summary

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from a CMC perspective pending an acceptable recommendation from the Office of Compliance and the microbiology reviewer.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase 4 activity recommendations

II. Summary of Chemistry Assessments

Calcium chloride dihydrate, sodium chloride, magnesium chloride hexahydrate, sodium bicarbonate, potassium chloride, and dibasic sodium phosphate were identified as drug substances in this application. All drug substances are compendial grade, though these components are typically used as excipients. The applicant includes pertinent information pertaining to the manufacture and control of each of the drug substances including the manufactures, acceptance criteria, certificates of analyses and methods of manufacture in this application as well as DMF references

(b) (4)

(b) (4)

The respective DMFs were reviewed in conjunction with this application and were found adequate to support the approval of this NDA.

The drug product is clear sterile, bicarbonate infusate solution. The drug product will be used as replacement solutions in hemofiltration (HF) and hemodiafiltration (HDF) procedures during continuous renal replacement therapy (CRRT). The drug product is presented in two different formulations (BK4/2.5 and B22K4/0) and is provided in a pre-packaged, five liter, two compartment polyvinylchloride bag. The smaller compartment has a 250 mL capacity and contains the electrolyte solution. The larger compartment contains the buffer solution and has a capacity of 4,750 mL. The two compartments are used

(b) (4)

(b) (4) The exact compositions of the electrolyte and buffer solutions are included in the table below.

Drug Product Composition Before Reconstitution

Executive Summary Section

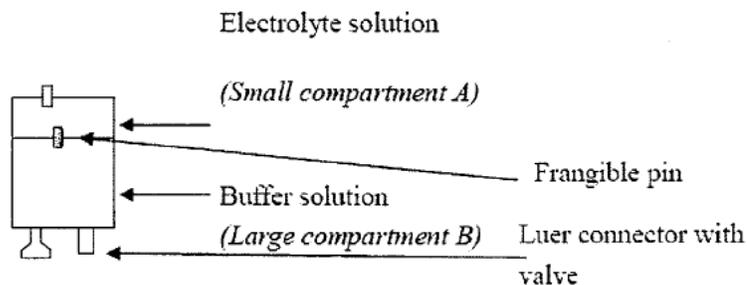
BEFORE RECONSTITUTION (g/L)	Phoxilium BK4/2.5	Phoxilium B22K4/0
	Small compartment A (250 ml)	
Calcium chloride, 2 H ₂ O	3.68	0
Magnesium chloride, 6 H ₂ O	3.05	3.05
Excipient: Water for injection q.s. to 1000 ml*. Hydrochloric acid to adjust pH (before sterilization)		
Large compartment B (4 750 ml)		
Sodium chloride	6.34	6.95
Sodium bicarbonate	3.09	2.21
Potassium chloride	0.314	0.314
Dibasic sodium phosphate	0.187	0.187
Excipient: Water for injection q.s. (b) (4) Carbon dioxide to adjust pH (b) (4)		

After Reconstitution

(in mEq/L except where noted)	Phoxilium BK4/2.5	Phoxilium B22K4/0
Sodium Na ⁺	140	140
Potassium K ⁺	4.0	4.0
Calcium Ca ²⁺	2.5	0
Magnesium Mg ²⁺	1.5	1.5
Chloride Cl ⁻	114.5	122.0
Phosphate HPO ₄ ²⁻	1 mmol/L	1 mmol/L
Bicarbonate HCO ₃ ⁻	32	22
Theoretical Osmolarity	(b) (4) mOsm/L	290 mOsm/L

The two compartment container closure system includes 3 ports and one breakable frangible pin (see figure below). (b) (4) the bags will be overwrapped (b) (4)

Reconstitution of the drug product is achieved by breaking the frangible pin which is contained between the two compartments.



The drug product will be manufactured and packaged by Gambro Renal Products of Daytona Beach, FL and stability testing will be completed by Gambro BCT of

Executive Summary Section

Lakewood, CO. The manufacturing process for this drug product is (b) (4).
(b) (4) The batch size for the buffer solution will range from (b) (4) L
and the batch size for the electrolyte solution will range from (b) (4) L. These
batch sizes will result in between (b) (4) bags of the drug product.

Grambro has requested a 12 month shelf life for the drug product and a 24 hour expiry for the reconstituted solution. Grambro has not manufactured the to-be-marketed drug product formulations (BK4/2.5 and B22K4/0). Stability data and batch analyses were submitted for two other formulations, (b) (4).
(b) (4) Both the (b) (4) formulations have the same components BK4/2.5 and B22K4/0. After reconstitution, the (b) (4) formulation is identical to the BK4/2.5 formulations. The applicant included 12 months of long term and 6 months accelerated primary stability data for three batches each of the (b) (4) (b) (4) formulations packaged in the commercial container closure system. The stability protocol utilized a matrixing approach. In addition to the primary stability data, the applicant provided in-use stability data to demonstrate that the reconstituted drug product is stable at room temperature for up to 24 hours after reconstitution. All data was acceptable and within the prescribed acceptance criteria. Accordingly, the **12 month expiry** is granted. The applicant also requested a 24-hour expiry for the reconstituted drug product. The reconstituted solutions were tested after 0, 18 and 24 hours at room temperature. All data for the reconstituted solution were acceptable and within the prescribed acceptance criteria, accordingly the **24-hour expiry for the reconstituted** solution is granted.

B. Description of How the Drug Product is Intended to be Used

The drug product is being developed for use as replacement solutions in hemofiltration (HF) and hemodiafiltration (HDF) procedures during continuous renal replacement therapy (CRRT).

The drug product will be packaged as a monodose presentation in a sterilized two compartment PVC bag that has a total capacity of 5000 mL. The smaller compartment (compartment A) has a 250 mL capacity and contains the electrolyte solution. The electrolyte solution consists of USP grade calcium chloride and magnesium chloride in water for injection with hydrochloric acid to adjust the pH. The larger compartment (compartment B) has a 4750 mL capacity and contains the buffer solution. The buffer solution consists of USP grade sodium chloride, sodium bicarbonate, potassium bicarbonate, dibasic sodium phosphate in water for injection with carbon dioxide to adjust the pH. The two compartment packaging system contains a red frangible pin that is located between the two compartments and is broken immediately prior to use to reconstitute the final drug product. (b) (4)

(b) (4) Reconstitution instructions are clearly spelled out in the "Direction for Use" section of the package insert.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is recommended for approval pending an acceptable recommendation from the Office of Compliance. The drug substances were determined to be safe, effective, and manufactured in a consistent manner with inherent quality in the respective DMFs and in this application. The sponsor identified CQA and established controls to ensure the quality of the drug product. The results of the batch analyses confirm quality of the drug product at release. The intended commercial packaging presentations has been previously used in approved products provide adequate protection of the drug product and ensure drug product quality over the proposed 12-month shelf-life as demonstrated through the drug product stability data. With the exception of the ^{(b) (4)} statement, the draft labels and package insert are acceptable from a CMC perspective.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

OStephens

C. CC Block

Orig. NDA 207026

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CMC and Biopharmaceutics
NDA 207026, Phoxilium

IQA and Filing Review Cover Sheet

1. **NEW DRUG APPLICATION NUMBER:** 207026

2. **DATES AND GOALS:**

Letter Date:	13-Mar-2014
Filing:	12-May-2014
Filing 74 Day Issues:	26-May-2014
PDUFA Goal Date:	13-Jan-2015

3. **PRODUCT PROPERTIES:**

Trade or Proprietary Name:	Phoxilium (proposed)
Established or Non-Proprietary Name (USAN):	
Dosage Form:	Sterile solution
Route of Administration	In the extracorporeal circuit for CRRT
Strength/Potency	BK4/2.5 and B22K4/0 (see below)
Rx/OTC Dispensed:	Rx

After Reconstitution

(in mEq/L except where noted)		Phoxilium BK4/2.5	Phoxilium B22K4/0
Calcium	Ca ²⁺	2.5	0
Magnesium	Mg ²⁺	1.5	1.5
Sodium	Na ⁺	140	140
Chloride	Cl ⁻	114.5	122.0
Bicarbonate	HCO ₃ ⁻	32	22
Potassium	K ⁺	4.0	4.0
Phosphate	HPO ₄ ²⁻	1 mmol/L	1 mmol/L
Theoretical Osmolarity		294 mOsm/L	290 mOsm/L

4. **INDICATION:** Replacement solution in patients undergoing Continuous Renal Replacement Therapy (CRRT)

5. **DRUG SUBSTANCE STRUCTURAL FORMULA:**

NaCl; KCl; CaCl₂ .2H₂O; MgCl₂ .6H₂O; Na₂HPO₄ .2H₂O; NaHCO₃

6. **NAME OF APPLICANT (as indicated on Form 356h):**

Gambro Lundia AB



CMC and Biopharmaceutics

NDA 207026, Phoxilium

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DCRP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology

9. QUALITY REVIEW TEAM:

Discipline	Reviewer
CMC	Sherita McLamore, Ph.D.
Biopharmaceutics	Okpo Eradiri, Ph.D.
Microbiology	Denise Miller
Facilities	Vibhakar Shah, Ph.D.



CMC and Biopharmaceutics

NDA 207026, Phoxilium

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes

CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

No

CMC Comments for 74-Day Letter: None

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?

Yes

Biopharmaceutics Filing Issues:

None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?

No

Biopharmaceutics Comments for 74-Day Letter:

None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes

Microbiology Filing Issues: See filing review in DARRTS



CMC and Biopharmaceutics
NDA 207026, Phoxilium

Summary of Initial Quality Assessment

Table with 4 columns: Does the submission contain any of the following elements?, Nanotechnology, QbD Elements, PET, Other, please explain. Row 1: No, No, No, (blank). Row 2: (blank), (blank), (blank), (blank).

CMC Summary of Critical Issues and Complexities

Drug Substance:

- A number of DMFs are cited (b)(4); DMFs for (b)(4) have never been reviewed. DMF (b)(4) has been reviewed on 12 July, 2012 and found adequate. DMFs are not referenced for sodium bicarbonate and sodium chloride and the only CMC information on these is that provided in the NDA. It should also be noted that in the amendment dated Apr. 23, 2014, the Applicant states that the second suppliers originally listed for (b)(4) are not going to be used for registration and documentation provided for these are for information only.

Drug Product:

- The main issue with the product is that the Applicant has not manufactured the formulations they intend to market, but instead has leveraged their approved products, PrismaSol and PrismaSate for batch release and stability data. Data have been provided for 3 batches each of two formulations they call Phoxilium #1 (b)(4) and Phoxilium #2 (b)(4). Phoxilium #1 seems to be identical with the proposed Phoxilium BK4/2.5 formulation for marketing in this NDA; however, Phoxilium #2 is different in (b)(4) composition. These batches were manufactured in (b)(4), presumably for other applications and it is claimed that they bracket the formulations in this NDA. The lack of data for the to-be marketed solutions was discussed at the Branch and Division level and it was decided that this would not be a filing issue since the manufacturing process (b)(4) and stability is not expected to be affected by the differences.
In view of the above concerns, it is important to evaluate the post-approval stability commitment and request a revision, if needed.
What is the limiting factor in the stability of these solutions? As mentioned earlier, stability studies were carried out for 12 months at long term storage conditions for batches manufactured in (b)(4). It doesn't appear that the studies were continued beyond 12 months and the Applicant seems satisfied with a 12 month expiration dating period.



CMC and Biopharmaceutics

NDA 207026, Phoxilium

Labeling:

- The use of [REDACTED] ^{(b) (4)} on container labels and the PI is not acceptable and should be revised according to current policy.

Quality Assessment

This is a 505(b)(2) NDA for replacement solutions in patients undergoing Continuous Renal Replacement Therapy (CRRT). CRRT is a short term treatment and is considered a life-saving technique used in intensive care units. This application has only a quality section because of its similarity to the approved PrismaSol Solutions (NDA 21-703) which documented the extensive clinical and non-clinical literature data available to demonstrate the safety and efficacy of these products. The difference between PrismaSol solutions and Phoxilium solutions is the absence of dextrose and lactate in the latter and the absence of phosphate in the former. The other inorganic ions are common to both although concentrations may vary. No meetings were held with the Applicant prior to this submission.

Drug Substance: The drug substances present in Phoxilium solutions are calcium chloride, magnesium chloride, sodium chloride, sodium bicarbonate, potassium chloride and dibasic sodium phosphate. DMF references are provided for most of the drug substances except for one supplier, (b) (4)

(b) (4) In all cases a short description and flow diagram of the manufacturing process is provided in section 3.2.S along with specifications (mostly USP) and batch analysis data. No stability data are available for sodium chloride and sodium bicarbonate. Two manufacturers were originally listed for (b) (4); however, it was clarified in an amendment dated April 23, 2014, that (b) (4)

(b) (4) will not be used for registration purposes.

Drug Product: Phoxilium solutions are filled in a two-compartment bag, a small compartment (250 mL) containing the electrolyte solution and a large compartment (4750 mL) containing the buffer solution. One red frangible pin is located between the two compartments which has to be broken to mix the two solutions to give the final reconstituted solution for patient use. There are two “strengths” of the product which vary in the composition of some of the salts. The Applicant refers to these two presentations as BK 4/2.5 and B22K4/0. The small compartment contains calcium chloride dihydrate and magnesium chloride hexahydrate whereas the large compartment contains sodium chloride, sodium bicarbonate, potassium chloride and dibasic sodium phosphate with water for injection to obtain the desired volume. Hydrochloric acid is used (b) (4) to adjust pH prior to sterilization and carbon dioxide (b) (4)

The manufacturing process (b) (4)

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(b) (4)

The container closure system is a two compartment PVC bag

(b) (4)

The container is
overwrapped (b) (4)

Specifications are provided and include the customary attributes for parenteral products, i.e. sterility, particulate matter, endotoxins, pH etc. in addition to assay for the various ions, sodium, magnesium, potassium, calcium, bicarbonate and phosphate. Batch analysis results have been submitted for three batches each of two formulations, (b) (4). After reconstitution, the (b) (4) formulation (b) (4) seems to be identical to the BK4/2.5 formulation intended for marketing; however, the (b) (4) formulation (b) (4) differs from the other strength proposed for marketing, B22K/4.0 (b) (4). These batches were manufactured in (b) (4) so the assumption is that they were also used to support other applications. Stability studies have been performed on the same batches of the (b) (4) formulations packaged in the to-be-marketed 2 compartment bags. Since no degradation of the inorganic salts is expected, the main goals of the study were to follow water evaporation and carbon dioxide elimination from the overwrapped PVC bags to establish the stability of bicarbonate in a PVC bag. The Applicant states that a bracketing strategy was employed although this seems to refer to Phoxilium solutions that are not part of this application. The batch sizes are (b) (4) L for the buffer solution and (b) (4) L for the electrolyte solution which is stated to be the minimum production lot size. 12 months of long term data at 30° C/65% RH and 9 months of data at accelerated conditions. 40° C/40% RH, are available. A matrixing protocol at the 3 and 9 month time points in the long term study is used. The separate compartments (large and small) are tested for pH, color, clarity and particulate matter whereas after reconstitution, in addition to these attributes, assays for sodium, potassium, phosphate, calcium, magnesium and bicarbonate are performed. Bacterial endotoxins, sterility, permeability, extractable volume and DEHP are also monitored. Based on the data submitted a 12 month shelf-life for storage at controlled RT is proposed.

The Applicant has also performed studies at 0, 18 and 24 hours on the reconstituted solution to assess how long this solution is stable after mixing. These studies were carried out on product that had been aged for 0, 3 and 6 months under accelerated conditions and 6 and 12 months under long term conditions. Based on the results, the following in-use conditions are recommended for labeling: (b) (4)



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[Redacted] (b) (4)
”.

Additional Comments: Facilities for the manufacture of the drug substances and drug product have been entered into the EES database after receiving the revised 356h form. Methods Validation by FDA Laboratories will not be initiated at this time since this is not an NME. A categorical exclusion from Environmental Assessment has been requested by the Applicant.

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Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

Background: The proposed drug product comprises two pre-packaged sterile solutions for use as replacement solutions in hemofiltration and hemodiafiltration procedures during continuous renal replacement therapies (CRRT). The solutions contained in the small compartment (electrolyte solution) and in the large compartment (buffer solution) are sterile solutions and must be mixed immediately prior to use.

Submission: Only CMC data are submitted in this NDA.

Review: There are no Biopharmaceutics issues for review in this NDA.

Recommendation: No further action is warranted from Biopharmaceutics.

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CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Incomplete information in original 356 h. Amendment received
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA



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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	
10	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)

	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Reference to DMFs
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Reference to DMFs
14.	Does the section contain information regarding the characterization of the DS?	X		Reference to DMFs
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		References to DMFs
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			NA
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		



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H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	May 18, 2006	
	II		Feb. 11, 2013		
	II		Feb. 11, 2013		
	II		May 18, 2006		
	II		Jan. 9, 2013		
	II		Sep. 23, 2013		
	III		June 18, 2013		

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

Biopharmaceutics Filing Review Checklist

The following parameters are usually necessary to initiate a full Biopharmaceutics review (i.e., the NDA is complete enough to review but may have deficiencies). On **initial** overview of the NDA application for filing:

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?		X	
34.	Is the dissolution test part of the DP specifications?		X	
35.	Does the application contain the dissolution method development report?		X	
36.	Is there a validation package for the analytical method and dissolution methodology?		X	
37.	Does the application include a biowaiver request?		X	
38.	Are there adequate data supporting the waiver?			N/A
39.	Does the application include an IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is information on mixing the product with foods or liquids included?		X	
42.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	
FILING CONCLUSION				
43.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?			N/A



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J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
44.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
45.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
46.	Are there any potential review issues identified?		X	

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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

/s/

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