

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022581Orig1s000**

**CHEMISTRY REVIEW(S)**



**NDA 22-581**

**Phoslyra™**

**Fresenius Medical Care North America**

**Division of Cardiovascular and Renal Product**

**Julia C. Pinto, Ph.D.**

**Branch VII, Pre-Marketing Division III  
Office of New Drug Quality Assessment**

**For  
Division of Cardiovascular and Renal Products**



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## Chemistry Review Data Sheet

## Chemistry Review Sheet

1. NDA 22-581
2. REVIEW #: 2
3. REVIEW DATE: April 2, 2011
4. REVIEWER: Julia C. Pinto, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

July 20, 2009

## 6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed

Amendment

Amendment

Amendment

Document Date

August 2, 2010

October 18, 2010

February 17, 2011

## 7. NAME AND ADDRESS OF APPLICANT:

Name: Fresenius Medical Care North America  
Address: 920 Winter Street  
Waltham, MA 02451-1457

Representative: J. Claude Miller  
Vice President, Regulatory Affairs  
Fresenius Medical Care North America  
920 Winter Street  
Waltham, MA 02451

Telephone: (781) 699-2230

## 8. Product Drug Code and Name:

a) Proprietary Name: Phoslyra™

b) Non-Proprietary Name (USAN): Calcium Acetate Oral Solution

c) Code name/#(ONDQA only):

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 3
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## Chemistry Review Data Sheet

10. PHARMACOLOGICAL CATEGORY: Control of hyperphosphatemia in patients with end stage renal disease (ESRD)

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 667mg/5ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

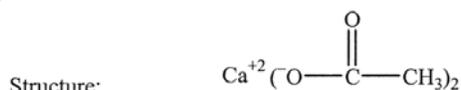
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Calcium Acetate, USP



Molecular Formula:  $\text{CaC}_4\text{H}_6\text{O}_4$

Molecular Weight: 158.17

17. RELATED/SUPPORTED DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code <sup>1</sup>	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Calcium Acetate	1	Adequate	8/31/2009	Anil Pendse, Rev #6

<sup>1</sup> 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



## Chemistry Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> 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
none		

## 18. Status

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	adequate	March 14 2011	Office of Compliance
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC	NA		
EA	Categorical exclusion satisfactory	July 14, 2009	
Microbiology	NA		

## Executive Summary Section

**The Chemistry Review for NDA** (b) (4)**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The Applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product in the original submission of July 20, 2009 (see review #1). All DMFs are recommended as adequate. However an overall recommendation by the Office of Compliance was pending and is now resolved. All facilities are recommended as adequate. Labels have adequate information as required. There are no further CMC or Compliance issues and this NDA is recommended for approval.

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

No Post Approval commitments are required.

**II. Summary of Chemistry Assessment****A. Description of Drug Substance and Drug Product:**

This submission (eCTD format) provides for a new liquid formulation of calcium acetate, that is to be marketed in addition to the currently approved Gelcap (PhosLo®, NDA 21-160) and Tablet (PhosLo®, NDA 19-976) formulations. The proposed indication for the liquid formulation is the same as that approved for the GelCaps and Tablets, which is for the control and treatment of hyperphosphatemia in patients with end stage renal disease (ESRD).

The calcium acetate drug substance, used in all three formulations, is referenced to DMF (b) (4) and has been reviewed as adequate by A. Pendse, Ph.D., (Review #6, August 31, 2009). No additional information or changes are submitted since the last review.

The drug product is manufactured as an oral solution containing (b) (4) maltitol, glycerin, propylene glycol, magnasweet 110, sucralose, methylparaben, povidone and cherry and menthol flavorings. The bulk solution will be packaged in both (b) (4) 16 oz amber polyethylene bottles.

Stability studies demonstrate the drug products to be stable, without degradation through at least 12 months under long term and accelerated conditions. Consequently, a 24 month expiration is given to this product.

**Description of How the drug is intended to be used:**

Phoslyra® Oral Solution is pale green-yellow clear liquid formulation of calcium acetate to be used as phosphate binder, to control hyperphosphatemia in patients with end stage renal disease. This product is designed to be bioequivalent to the Phoslo® tablets. The solution is supplied in (b) (4) 16 oz bottles, stored at 25°C (77°F) with excursions permitted to 15° to 30°C (59° to 86°F) . Proposed Expiry is 24 months.

## Executive Summary Section

**C. Basis for Approvability Recommendation**

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required. All DMFs are recommended as adequate. OC has recommend all facilities as adequate. From the CMC perspective, this NDA is recommended for "Approval" with a 24 month expiration dating period and storage at 25°C/60%RH.

**III. Administrative****A. Reviewer's Signature**

Julia C. Pinto, Ph.D.

**B. Endorsement Block**

Ramesh Sood, PhD, Branch Chief

**C. CC Block**

Pharmaceutical Assessment Leader: Kasturi Srinivasachar, Ph.D.

Project Manager: Lori Wachter

9 Pages of Draft  
Labeling have been  
Withheld in Full as b4  
(CCI/TS) immediately  
following this page

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/s/  
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JULIA C PINTO  
04/06/2011

RAMESH K SOOD  
04/06/2011

## **MEMO TO FILE**

**Application Number:** NDA 22581  
**Submission Date:** July 21, 2009  
**Date:** May 6, 2010

The Office of Compliance (OC) has given an overall recommendation of withhold, for this NDA application. The EES report is attached below.  
Two of the manufacturing facilities have been issued a withhold after inspection by OC.

During the inspection of (b) (4), the drug substance manufacturer, OC found that an additional laboratory is used for some of the release testing. Neither the Sponsor nor the Agency were aware of the ongoing testing at the new facility. It is expected that an amendment to this NDA will be filed, adding (b) (4) (b) (4), as an additional testing facility for the drug substance manufactured at (b) (4).

The drug product manufacturer, Lyne Laboratories, was inspected twice by OC, and continued deficiencies were found and sited on form 483. Re-inspection of this facility will be done upon resolution of the 483 deficiencies.

Therefore, from the CMC standpoint, this NDA is recommended as a complete response, pending resolution of the compliance issues.

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 22581/000	<b>Sponsor:</b>	FRESENIUS
<b>Org. Code:</b>	110		920 WINTER ST
<b>Priority:</b>	3		WALTHAM, MA 02451
<b>Stamp Date:</b>	21-JUL-2009	<b>Brand Name:</b>	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/
<b>PDUFA Date:</b>	21-MAY-2010	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	CALCIUM ACETATE ORAL SOLUTION 667MG/5ML
<b>District Goal:</b>	22-MAR-2010	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; SOLUTION; CALCIUM ACETATE; 667MG/5ML
<b>FDA Contacts:</b>	J. PINTO	<b>Review Chemist</b>	301-796-1733
	N. CHIDAMBARAM	<b>Team Leader</b>	301-796-1339

**Overall Recommendation:** WITHHOLD on 05-MAY-2010 by M. STOCK (HFD-320) 301-796-4753

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** SALEM, NH 030792837  
**Responsibilities:** (b) (4) **AADA:**  
**Profile:** **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 24-AUG-2009  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** **AADA:**  
**Responsibilities:** (b) (4)  
**Profile:** **OAI Status:** POTENTIAL OAI

**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 05-MAY-2010  
**Decision:** WITHHOLD  
**Reason:** DISTRICT RECOMMENDATION

**Establishment:** CFN: 1224701 FEI: 1000513191  
LYNE LABORATORIES INC  
10 BURKE DR  
BROCKTON, MA 02301

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS, OAI Status: POTENTIAL OAI

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 04-MAY-2010

**Decision:** WITHHOLD

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** (b) (4)

**Profile:** OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 24-AUG-2009

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** (b) (4)

**Profile:** OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11-JAN-2010

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22581	ORIG-1	FRESENIUS BIOTECH NORTH AMERICA INC	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/

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

/s/

JULIA C PINTO  
05/10/2010

RAMESH K SOOD  
05/10/2010



# CHEMISTRY REVIEW



**NDA 22-581**

**Phoslyra<sup>TM</sup>**

**Fresenius Medical Care North America**

**Division of Cardiovascular and Renal Product**

**Julia C. Pinto, Ph.D.**

**Branch VII, Post Marketing Division IV  
Office of New Drug Quality Assessment**

**For  
Division of Cardiovascular and Renal Products**

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P DRUG PRODUCT [Phoslyra® Oral Solution, Fresnius .....	15
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III. <b>List Of Deficiencies To Be Communicated .....</b>	

## Chemistry Review Data Sheet

**Chemistry Review Sheet**

1. NDA 22-581
2. REVIEW #: 1
3. REVIEW DATE: December 20, 2009
4. REVIEWER: Julia C. Pinto, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

N/A

## 6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Document Date

July 20, 2009

## 7. NAME AND ADDRESS OF APPLICANT:

Name: Fresenius Medical Care North America  
Address: 920 Winter Street  
Waltham, MA 02451-1457

Representative: J. Claude Miller  
Vice President, Regulatory Affairs  
Fresenius Medical Care North America  
920 Winter Street  
Waltham, MA 02451

Telephone: (781) 699-2230

## 8. Product Drug Code and Name:

- a) Proprietary Name: Phoslyra™
- b) Non-Proprietary Name (USAN): Calcium Acetate Oral Solution
- c) Code name/(ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: Type 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## Chemistry Review Data Sheet

10. PHARMACOLOGICAL CATEGORY: Control of hyperphosphatemia in patients with end stage renal disease (ESRD)

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 667mg/5ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

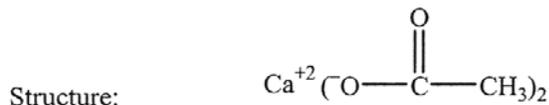
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product Form Completed

Not a SPOTS product

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

Calcium Acetate, USP



Molecular Formula:  $\text{CaC}_4\text{H}_6\text{O}_4$

Molecular Weight: 158.17

17. RELATED/SUPPORTED DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code <sup>1</sup>	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Calcium Acetate	1	Adequate	8/31/2009	Anil Pendse, Rev #6

<sup>1</sup> 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

Chemistry Review Data Sheet

- 6 DMF not available
- 7 Other (explain under "Comments")

<sup>2</sup> 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
none		

18. Status

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		Office of Compliance
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC	NA		
EA	Categorical exclusion satisfactory	July 14, 2009	
Microbiology	NA		

## Executive Summary Section

**The Chemistry Review for NDA (b) (4)****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required, pending one modification as detailed in the labeling section below. All DMFs are recommended as adequate. An overall recommendation by the Office of Compliance is pending. There are no CMC issues and a final recommendation for this NDA will be made once OC has issued an overall recommendation.

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

No Post Approval commitments are required.

**II. Summary of Chemistry Assessment****A. Description of Drug Substance and Drug Product:**

This submission (eCTD format) provides for a new liquid formulation of calcium acetate, that is to be marketed in addition to the currently approved Gelcap (PhosLo®, NDA 21-160) and Tablet (PhosLo®, NDA 19-976) formulations. The proposed indication for the liquid formulation is the same as that approved for the GelCaps and Tablets, which is for the control and treatment of hyperphosphatemia in patients with end stage renal disease (ESRD).

The calcium acetate drug substance, used in all three formulations, is referenced to DMF (b) (4) and has been reviewed as adequate by A. Pendse, Ph.D., (Review #6, August 31, 2009). No additional information or changes are submitted since the last review.

The drug product is manufactured as an oral solution containing (b) (4) maltitol, glycerin, propylene glycol, magnasweet 110, sucralose, methylparaben, povidone and cherry and menthol flavorings. The bulk solution will be packaged in both (b) (4) 16 oz amber polyethylene bottles.

Stability studies demonstrate the drug products to be stable, without degradation through at least 12 months under long term and accelerated conditions. Consequently, a 24 month expiration is given to this product.

**Description of How the drug is intended to be used:**

Phoslyra® Oral Solution is pale green-yellow clear liquid formulation of calcium acetate to be used as phosphate binder, to control hyperphosphatemia in patients with end stage renal disease. This product is designed to be bioequivalent to the Phoslo® tablets. The solution is supplied in (b) (4) (b) (4) and 16 oz bottles, stored at 25°C (77°F) with excursions permitted to 15° to 30°C (59° to 86°F) . Proposed Expiry is 24 months.

## Executive Summary Section

**C. Basis for Approvability Recommendation**

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required, pending one modification as detailed in the labeling section below. All DMFs are recommended as adequate. From the CMC perspective, this NDA is recommended for "Approval" with a 24 month expiration dating period and storage at 25°C/60%RH. However a final recommendation will be made once OC has issued an overall recommendation.

**III. Administrative****A. Reviewer's Signature**

Julia C. Pinto, Ph.D.

**B. Endorsement Block**

Ramesh Sood, PhD, Branch Chief

**C. CC Block**

Pharmaceutical Assessment Leader: Kasturi Srinivasachar, Ph.D.

Project Manager: Lori Wachter

26 Pages of Draft Labeling have been Withheld  
in Full as b4 (CCI/TS) immediately following  
this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22581	ORIG-1	FRESENIUS BIOTECH NORTH AMERICA INC	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/

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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.**

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/s/

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JULIA C PINTO  
03/31/2010

KASTURI SRINIVASACHAR  
03/31/2010

## Initial Quality Assessment Branch I

<b>OND Division:</b>	Division of Cardiovascular and Renal Products
<b>NDA:</b>	22-581
<b>Applicant:</b>	Fresenius Medical Care North America
<b>Letter Date:</b>	20 July 2009
<b>Status Date:</b>	21 July 2009
<b>PDUFA Date:</b>	21 May 2010
<b>Tradename:</b>	Phoslyra
<b>Established Name:</b>	Calcium Acetate
<b>Dosage Form:</b>	Oral solution, 667mg/5mL
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Control of hyperphosphatemia in patients with End Stage Renal Disease
<b>Assessed by:</b>	Kasturi Srinivasachar
<b>ONDQA Fileability:</b>	Yes

### Summary

This paper NDA, in eCTD format, is for a new liquid formulation of calcium acetate, a phosphate binder. Solid oral dosage forms of calcium acetate have been marketed under the tradename PhosLo as tablets (NDA 19-976) and gelcaps (NDA 21-160) since 1990 and 2001 respectively. The tablet formulation is no longer marketed for business reasons since it was found that the gelcap formulation had superior compliance and palatability. The proposed indication for this NDA is the same as for PhosLo for which an orphan drug designation has been granted (b) (4)

In support of this NDA, a bioequivalence study comparing the liquid formulation with PhosLo gelcaps was carried out under IND (b) (4). A meeting was held on Dec.12, 2006 with Nabi Biopharmaceuticals, owner of NDA 21-160 at that time, to discuss requirements for the liquid formulation. CMC representatives from ONDQA's post-marketing division informed the applicant that (b) (4)

(b) (4) a new NDA would be needed. They also noted that shelf-life for the product would be determined by the provided stability data, in response to the Applicant's proposal to submit 3 months' data at the time of filing and an additional 3 months during the review cycle to support an expiration date of 24 months. Nabi was advised to demonstrate the preservative effectiveness of methylparaben at the range proposed for the stability acceptance criteria. In view of (b) (4) (b) (4) in the original formulation, Fresenius revised the formulation to replace this excipient with maltitol and a t-con was held on Jan 31, 2008 to further discuss inter-disciplinary issues. The postmarketing division of ONDQA continued to be involved in these discussions which primarily focused on the use of maltitol which was claimed to be GRAS. The applicant was asked to submit CMC information on the flavoring agents used in the formulation or cross-references to DMFs. A temperature cycling stability study to determine if there were any viscosity changes in the formulation was also recommended. Subsequent meetings with the Applicant do not appear to have a CMC component.

## Drug Substance

The drug substance, calcium acetate USP, is the same as used in the approved solid dosage form NDAs 19-976 (tablets) and 21-160 (gelcaps). It is a white powder (b) (4) which is soluble in water. It is manufactured by (b) (4) Type II DMF (b) (4) has been referenced for complete information on the manufacturing and controls of calcium acetate. This DMF has been reviewed previously and the last review dated Aug. 18, 2009 deemed it to be adequate. The specification follows the USP monograph which, as expected, lists limits for a number of inorganic impurities. Only one lot of drug substance has been used in the manufacture of the 3 finished product batches used to support this application. A lot of historical data exists for calcium acetate but recently, a formal ICH stability program was initiated with 3 batches and data for 6 months at long term and accelerated conditions are available. An expiration dating period of (b) (4) is claimed.

## Drug Product

The drug product is an oral solution that is formulated at a strength of 667mg/5mL as a pale to light greenish-yellow clear liquid with cherry odor. In addition to standard compendial excipients, it contains an artificial black cherry flavor, menthol natural flavor and magnasweet 110, all of which are non-compendial. Methylparaben is used as a preservative. The formulation was designed to be bioequivalent with the approved PhosLo tablets and gelcaps and to contain the same amount (667 mg) of calcium acetate in 5 mL as one tablet or gelcap. Formulation development focused on palatability and chemical and physical stability. (b) (4) which was initially included (b) (4), was replaced with maltitol (b) (4). The formulations of the clinical and stability batches are identical with the final product formulation intended for marketing.

The manufacturing process (b) (4)

Product specifications have been proposed and include the customary test attributes for an oral solution. Batch analysis data for 3 pilot scale batches have been provided. Stability studies have been carried out on the same batches under ICH accelerated, long term and refrigerated conditions and 6, 12 and 12 months' data, respectively, are available. A freeze-thaw and elevated temperature study was also performed to establish that shipping conditions do not adversely affect the product. An expiration dating period of 24 months is proposed for storage under controlled room temperature conditions.

## Critical Review Issues

### Drug substance

- Can an expiration dating period of (b)(4) be granted for calcium acetate on the basis of historical data and 6 months of long term and accelerated stability data under ICH conditions?
- Does the Applicant distinguish between retest date and expiration date?

### Drug Product

- Has sufficient information been submitted, either in the NDA or in DMFs, for the 3 non-compendial excipients to provide assurance of their identity, quality and purity?
- Are the proposed specifications for the non-compendial excipients adequate?
- The USP monograph for calcium acetate tablets lists a test for aluminum even though this is also in the substance monograph. Is a test for aluminum needed for the oral solution dosage form as well?
- The product specification does not have a test for either specific gravity or viscosity. Is this acceptable?
- Has the effectiveness of methylparaben been adequately demonstrated at the lowest shelf-life limit?
- Is it acceptable not to test the drug product for impurities on release or during stability studies?
- Has the container closure system been tested for leachables / extractables? Is this a concern for this oral solution?
- The postapproval stability commitment for the first 3 production batches does not seem to include studies under accelerated storage conditions.
- In vitro dissolution studies that have been performed to compare this dosage form with the marketed PhosLo product should be consulted to the Biopharmaceutics group in ONDQA.

### Labeling

- The strength is listed everywhere as 667mg/5mL is this acceptable?

### Comments and Recommendations

The NDA was filed before the application was received by this PAL because it was erroneously accepted for review by the Postmarketing Division of ONDQA. This is also the reason why this IQA is being written so late. This is a Type 3 (new dosage form) application which belongs to the Division of Premarketing Assessment. Manufacturing, testing and packaging facilities which were entered into EES were incomplete and revisions are currently being made. The reviewer should verify the accuracy and completeness of the entries. A reviewer was assigned by the Postmarketing Division who will continue the primary review of this NDA.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead  
Ramesh Sood, Ph.D.  
Branch Chief

Sep. 18, 2009  
Date  
Sep. 18, 2009  
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22581	ORIG-1	FRESENIUS BIOTECH NORTH AMERICA INC	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/

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

/s/

KASTURI SRINIVASACHAR  
09/18/2009

RAMESH K SOOD  
09/18/2009