CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022581Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 20, 2010
From	Rajanikanth Madabushi, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-581
Applicant	Fresenius Medical Care North America
Date of Submission	July 20, 2009
PDUFA Goal Date	May 21, 2010
Proprietary Name / Established (USAN) names	PHOSLYRA™ calcium acetate oral solution
Dosage forms / Strength	Oral Solution; 667 mg/5 mL
Proposed Indication(s)	Hyperphosphatemia in patients with end stage renal disease
Recommended:	*Approval pending the recommendation by Office of Compliance*

This secondary review is based, on the primary reviews of:

- Chemistry (Julia C. Pinto and Kasturi Srinivasachar), March 31, 2010
- Pharmacology/Toxicology (Patricia P. Harlow and Albert DeFelice), March 12, 2010 and March 15, 2010)
- CDRH Consults (Irada S. Isayeva, Dinesh Patwardhan and Courtney C. Harper), April 09, 2010
- Biometrics (Donald J. Schuirmann and Stella G. Machado), April 08, 2010
- Clinical (Gail I. Moreschi), February 2, 2010 and discussions with Abraham M.Karkowsky

Cross Discipline Team Leader Review Template

1. Introduction

In the current submission, Fersenius Medical Care North America is seeking for the approval of Phoslyra™, Calcium Acetate Oral Solution 667 mg/ 5 mL for the control of hyperphosphatemia in patients with end stage renal disease. Calcium acetate as solid dosage form is currently approved as PhosLo™ Tablets under NDA 19-976 in 1990 and PhosLo™ Gelcaps under NDA 21-160 in 2001. The potential advantages for developing a liquid formulation are reduction in the number of pills ingested, improved patient compliance by enhancing the palatability of calcium acetate, an alternative to crushing or chewing the solid dosage form, and to provide a dosage form for patients with swallowing difficulties.
The primary basis in support of this new drug application comes from a single clinical study (Study LP-RTG-01-01) aimed to evaluate the bioequivalence of Phoslyra™ compared to PhosLo™ Gelcaps with respect to urinary calcium and serum phosphorous. This approach was agreed upon by the Agency (Meeting Minutes dated 05/20/2009 IND (b) (4).

2. Background

As stated in Dr. Moreschi's review, 5 mL of the oral solution is to have the identical calcium acetate dosage contained in one tablet or gelcap. The efficacy of the two dosage forms from a phosphate binding aspect can be expected to be similar, hence, not requiring any dedicated efficacy studies. The only issue of concern with liquid dosage form is increased calcium absorption as calcium acetate is in a solution form.
The key issues that were discussed by the review team and considered important for determining the approvability are:

- Is Phoslyra™ associated with excess calcium absorption compared to PhosLo™ Gelcaps?
  - The general approach was to estimate the relative bioavailability of Phoslyra™ with regard to the extent of calcium absorption in contrast to the primary objective stated by the sponsor that seeks to evaluate bioequivalence. Since calcium occurs naturally in the body and is expected to have a time-course in response to the diet and physiological regulation, analyses were conducted on the baseline corrected measures. Results with regard to other metrics of exposure and those associated with phosphorous formed supportive evidence.
- Is there a potential safety concern associated with maltitol in Phoslyra™ that may alter the benefit-risk?
  - The two aspects that were explored to address this issue were: glycemic burden of absorbed maltitol and diarrhea due to the osmotic effects of unabsorbed maltitol.
- Does maltitol falsely register as "glucose" on a glucose meter and report spuriously high blood glucose test results?
  - The molecular structure aspects of maltitol and its metabolism products were studied to provide insights with regard to interference potential.

3. CMC/Device

CMC:
There are no unresolved CMC issues with regard to the drug substance and product. The recommendations with regard to two inspections from the Office of Compliance are pending.
The following information is obtained from the Chemistry Review by Julia C. Pinto and Kasturi Srinivasachar, March 31, 2010.

- General product quality considerations
  The calcium acetate drug substance, used in Phoslyra™ and PhosLo™ Gelcaps, 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, methylpar one and cherry and menthol flavorings.
  Calcium acetate is classified as GRAS according to 21CFR 582.1 and all excipients are compendial and in accordance with the Inactive Ingredient Guidelines (II-G) with the exception of the Cherry and Menthol flavorings which are also GRAS according to 21 CFR 582.20.
  The final product is a pale green-yellow clear liquid formulation. The bulk solution will be packaged in both (b) (4) and 16 oz amber polyethylene bottles, stored at 25ºC (77ºF) with excursions permitted to 15º to 30ºC (59º to 86ºF).
  Stability studies demonstrate the drug products to be stable, without degradation through at least 12 months under long term and accelerated conditions. Consequently, 24 month expiration is given to this product.

- Facilities review/inspection
  Two sites for inspection by Office of Compliance were requested:
  1. (b) (4) facility responsible for manufacture, packaging, labeling and release testing of calcium acetate drug substance.
     Current Status: Inspection of (b) (4) revealed that (b) (4) (b) (4) was involved in performing the release testing. This site was not reported by the sponsor in their submission and a communication with the sponsor revealed that they were not aware of (b) (4) involvement. It is not clear at this moment whether the inspection for (b) (4) is required or not *(See Appendix 1*).
  2. Lyne Laboratories, Inc. acceptance and stability testing was performed.
     Current Status: Inspection completed with a "withhold" status pending overall recommendation by Office of Compliance.

- Recommendation and Conclusion on Approvability (per The Chemistry Review)
  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.

CDRH Consults:
There are no unresolved issues with regard to potential interference with blood glucose meters. An Intercenter Consultative Review was requested regarding the use of maltitol as a sweetner in Phoslyra™. Some non-glucose sugars can falsely elevate results in blood glucose monitors utilizing glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) methodology.
This concern led to the request to investigate whether maltitol was absorbed and if so would it falsely register as "glucose" on a glucose meter. The following information is obtained from the CDRH Consult Review by Irada S. Isayeva, Dinesh Patwardhan and Courtney C. Harper, April 09, 2010.
The key findings are:

- Maltitol is unlikely, due to its molecular structure, to register on any glucose test strips as glucose.
- Maltitol is poorly absorbed into the blood and thus would not be present at high concentrations in blood samples. Given the low Glycaemic Index of maltitol the raise in blood glucose will be small and may not be detected on glucometers.
- When metabolized, maltitol is converted into glucose and sorbitol. Sorbitol would not interfere with glucose test results. Glucose, when present in the blood, would be appropriately measured by blood glucose meters regardless of the source.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical pharmacology/toxicology issues. The following information is obtained from the Pharmacology/Toxicology Review by Patricia P. Harlow and Albert DeFelice, March 12, 2010 and March 15, 2010.
The key review findings are:

- No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission. The sponsor referred to NDA 19-976 Volume 1.2 Section 314.50d(2) Nonclinical Pharmacology and Toxicology for Module 4 Nonclinical Study Reports and, if necessary, to relevant sections of NDA 21-160.
- Maltitol and maltitol syrups are self-affirmed GRAS based on petition to the FDA. The European Union's Scientific Committee on Food (SCF) and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) concluded that maltitol is safe and assigned the safest category of an acceptable daily intake (ADI) for maltitol of "not specified."
- The FDA "Inactive Ingredient list for Approved Products" (last updated January 13, 2010) indicates that maltitol is approved for oral administration in solution at a maximum potency of 65% (w/v). In contrast, PhosLo contains 20% maltitol (w/v).
- Two approved products Baraclude™ and Keppra™ contain high amounts of maltitol. The total daily doses contain 7.6 gm and 4.5 gm maltitol respectively. The total daily dose of maltitol for patients taking Phoslyra™ is 9 12 gm.
- Polyol sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Although the maximum recommended dosage

of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce laxative effects, maltitol is used in many food products and nutritional supplements, such as Nepro® designed specifically for patients with chronic kidney failure on dialysis. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

Based on this expectation, the Warnings and Precaution section of the label is updated with the following statement "May cause diarrhea with nutritional supplements which contain maltitol".

5. Clinical Pharmacology/Statistics

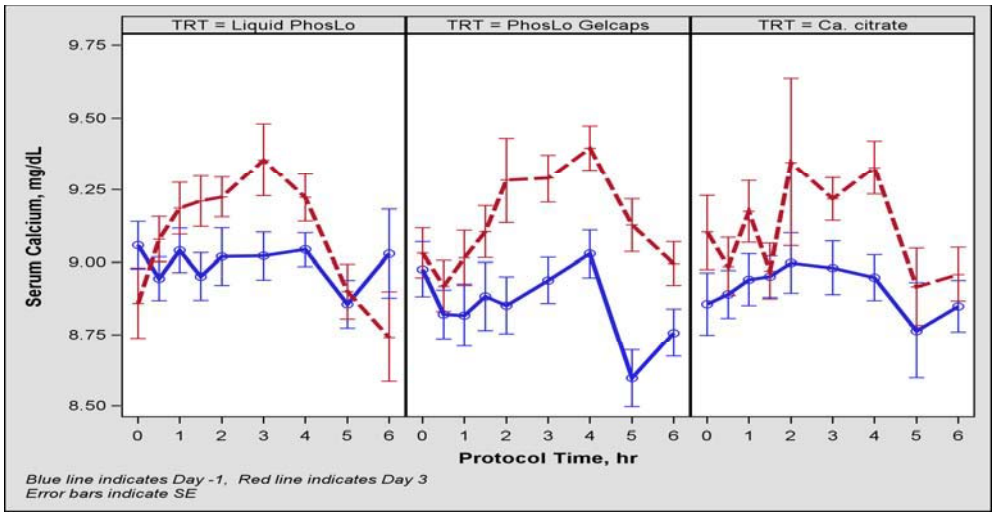
There are no unresolved clinical pharmacology/statistics issues.

The key issue in this review was to determine the relative bioavailability of Phoslyra™ when compared to PhosLo Gelcaps™ with regard to the rate and extent of calcium absorption. Since calcium occurs naturally in the body and is expected to have a time-course in response to the diet and physiological regulation, the Agency required analyses with and without baseline correction (Meeting Minutes April 22, 2009; IND (b) (4) The analyses plans were to be developed in consultation with Donald J. Schuirmann, Expert Mathematical Statistician (Meeting Minutes April 22, 2009).

A brief description of the study design and conduct are presented in Section 7 of this review. In the current section the key findings from the open label crossover bioequivalence (BE) study in healthy volunteers, comparing Phoslyra™ (Liquid PhosLo Oral Solution formulation of calcium acetate) versus PhosLo Gelcaps using calcium citrate as a positive control in healthy volunteers are presented.

The following information is partly obtained from the Statistics Review by Donald J. Schuirmann and Stella G. Machado, April 08, 2010. The key findings are:

- Serum and urinary calcium were measured by a validated atomic absorption spectroscopy method. The method was validated over a concentration range of 0.4 mg/L to 5 mg/L (Source: Sponsor's Clinical Study Report for Protocol LP-RTG-01-01; Appendix 7).
- Serum phosphorus levels were measured by a validated modification of the classical phosphomolybdate method. The assay was validated over a concentration range of 2.77 to 8.8 mg/dL. Phosphorus in urine was measured by a modified Fiske and Subbarow method. The method has been validated over a concentration range of 6.1 to 137.3 mg/dL (Source: Sponsor's Clinical Study Report for Protocol LP-RTG-01-01; Appendix 7).
- The time-course of serum calcium for all the three treatment arm are reasonably comparable as shown in the figure below:



- Serum calcium concentration (as measured by $AUC_{0\ 6\ hrs}$) was statistically significantly higher under treatment with calcium citrate than at baseline (p 0.03), establishing validity of the study.
- The mean baseline-subtracted $AUC_{0\ 6\ hrs}$ for the liquid formulation appears to be lower than for the gelcap formulation (estimated ratio of means 0.460), and based on the confidence interval it appears at worst to be comparable (upper 90% confidence bound on ratio of means 1.009). Similar results (Table 6 of the Statistics Review) were observed for the mean amount of urinary calcium excreted in 6 hours ($Ae_{0\ 6\ hrs}$). Further, the unadjusted ratio of geometric means for C_{max}, $AUC_{0\ 6\ hrs}$ and $Ae_{0\ 6\ hrs}$ showed the 90% confidence intervals within 80% -125% for the Liquid PhosLo Oral Solution compared to PhosLo Gelcaps (Source: Sponsor's Clinical Study Report for Protocol LP-RTG-01-01; Tables 15 and 17).
- The mean subtraction-adjusted $AUC_{0\ 6\ hrs}$ for the liquid formulation appears to be lower than for the gelcap formulation (estimated ratio of means 0.540 Table 2 of the Statistical Review); however the upper bound of 90% confidence interval is greater than 125% (158%). Similar results were observed for the urinary phosphorous data (Table 6 of the Statistical Review). It should be noted that this study was not designed to evaluate the phosphate lowering effect of the treatment arms.

Based on the above findings, the PhosLo liquid formulation can be expected to result in calcium absorption similar to that of PhosLo™ Gelcaps.

6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

7. Clinical/Statistical- Efficacy

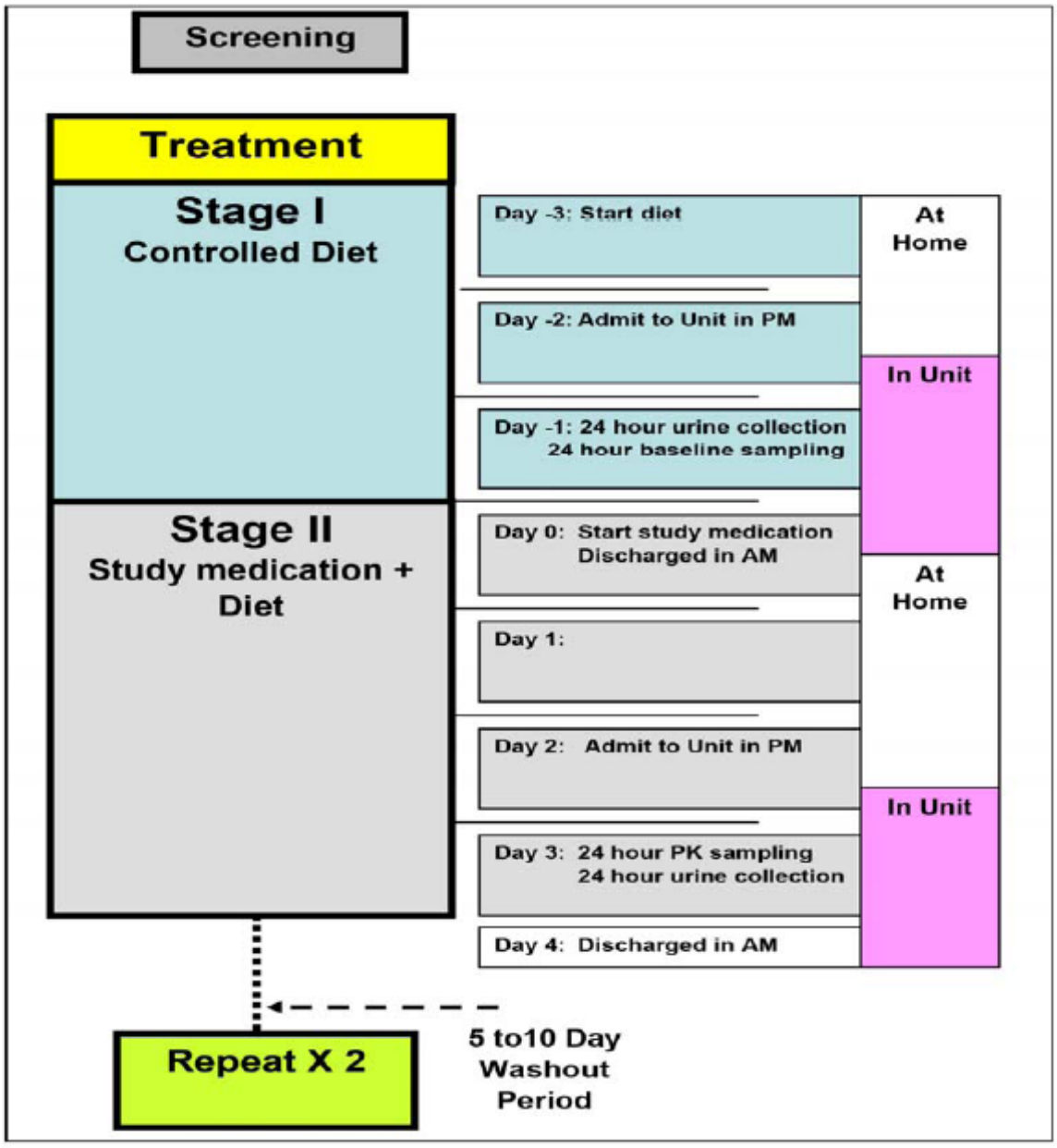
The primary basis in support of this new drug application comes from a single clinical study (Study LP-RTG-01-01) aimed to evaluate the bioequivalence of Phoslyra™ compared to PhosLo™ Gelcaps with respect to urinary calcium and serum phosphorous. This approach was agreed upon by the Agency (Meeting Minutes dated 05/20/2009 IND (b) (4). The

efficacy of the two dosage forms from a phosphate binding aspect can be expected to be similar, hence, not requiring any dedicated efficacy and safety studies.

The following information is obtained from the Clinical Review by Gail I Moreschi, February 2, 2010.

This study was designed as a randomized, controlled, 3-arm, open label, crossover Phase I study evaluating the bioequivalence of the investigational drug, liquid PhosLo compared to PhosLo Gelcaps. Calcium citrate provided a positive control profile for both the serum and urine 24 hr profiles. Approximately 40 subjects were planned to be enrolled. The primary objective was to demonstrate the bioequivalence of liquid PhosLo to PhosLo Gelcaps with respect to urinary calcium excretion and serum phosphorus level. Subjects who completed the tolerance test to oral liquid PhosLo were randomized (1:1:1) to 1 of 3 treatment sequences. The study included 4 periods as shown in the figure below. The sequential order of the 3 treatment periods (liquid PhosLo, PhosLo Gelcaps, and calcium citrate) was determined by randomization. Approximately the same amount of elemental calcium, 1000 mg, was administered in each dose for each treatment arm. Each treatment period was separated by a 5 to 10 day washout period. Each treatment period was divided into 2 stages. At Stage I, subjects were started on the controlled study diet. At Stage II, subjects were started on study medication and continued on the controlled study diet.

Study Design:



The treatment arms were:
A. 30 mL liquid PhosLo (667 mg calcium acetate/5 mL; 169 mg elemental calcium/5 mL),
B. 6 PhosLo Gelcaps (667 mg calcium acetate/gelcap; 169 mg elemental calcium/gelcap)
C. 5 calcium citrate caplets as a positive control (950 mg calcium citrate/caplet; 200 mg elemental calcium/caplet).
Evaluations included physical examination, vital signs, baseline serum measurement, 24 hr urine collection, 24 hr PK sampling, ECG and 6 hr serum glucose and insulin profile. PK levels were measured on pre-established study visits within each treatment period:

- Screening Period: Day -30 to Day -5
- Treatment Period Stage I: Day -3 to Day 0
- Treatment Period Stage II: Day 0 to Day 3

For the pharmacokinetic and statistical analyses, refer to Section 5.

8. Safety

- There were no deaths or serious adverse events (SAEs) during this study. There were also no AEs leading to withdrawal. Essentially, no drug-related safety concern was raised from the safety data in this study.
- Diarrhea occurred more frequently in the liquid PhosLo group compared to the PhosLo Gelcaps (5 subjects vs. 1 subject, respectively). The diarrhea was transient and resolved without sequlae.
- The analysis of the 6-hour glucose and insulin levels in serum did not indicate any significant influence of the maltitol in the liquid formulation on serum glucose control. The glucose and insulin responses were comparable between treatment groups.

9. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

10. Pediatrics

Current submission does not include any specific pediatric information. As stated in Dr. Moreschi's review, a liquid formula for PhosLo ultimately may be used in the pediatric population. Therefore, a Written Request must be encouraged although PhosLo received an Orphan Drug approval letter dated December 22, 1988.

11. Other Relevant Regulatory Issues

- Financial disclosures: There was nothing to disclose by the Principal Investigator or the five Sub-investigators (Gail I. Moreschi 4/15/2010)

12. Labeling

- **Proprietary Name:** The proposed proprietary name is Phoslyra (Calcium Acetate Oral Solution) 667 mg/5 mL. The Division of Medication Error Prevention and Analysis (DMEPA) requested a feedback from the Division regarding safety concerns if any with the use of dual trade names (Phoslyra and PhosLo) for calcium acetate. This issue was discussed at the Internal Meeting on 04/06/2010 and the review team concluded that **there was no potential safety issue associated with the dual trade names** (*see Appendix 2*).
  One of the potential concerns associated with dual trade names for the same product is overdosing resulting from both the products being accidently prescribed. The maximum dosage of phosphate binders are generally limited by the amount that can be consumed with every meal rather than dose limiting toxicity. Hence, this issue is not

of a concern in the present case. Further, different names for the two dosage forms is appropriate in the present situation as the liquid formulation may potentially be associated with laxative side effects that are not associated with the PhosLo™ Gelcaps. Currently a recommendation for the DMEPA is pending.

- At the time of this review, the following new elements were included in the label:
  - Warnings and Precaution and Adverse Reaction sections of the label are updated with the following statement "May cause diarrhea with nutritional supplements which contain maltitol"
  - Drug Interactions section is updated as follows: PHOSLYRA may decrease the bioavailability of tetracyclines or fluoroquinolones. There are no empirical data on avoiding drug interactions between PhosLo or PHOSLYRA and most concomitant drugs. When administering an oral medication with PHOSLYRA where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after PHOSLYRA or PhosLo. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.
  - The Pharmacodynamics section is updated to include the findings of Study LP-RTG-01-01.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval pending the results of the inspection and recommendations by the Office of Compliance.

- Risk Benefit Assessment

Phoslyra™ is an oral liquid dosage formulation of calcium acetate. The oral solution (5 mL) has identical calcium acetate dosage contained in one tablet or gelcap of PhosLo™. Hence, the efficacy of the two dosage forms from a phosphate binding aspect can be expected to be similar. The potential advantages for developing a liquid formulation are reduction in the number of pills ingested, improved patient compliance by enhancing the palatability of calcium acetate, an alternative to crushing or chewing the solid dosage form, and to provide a dosage form for patients with swallowing difficulties.

The potential risks associated with liquid dosage form are 1) increased calcium absorption as calcium acetate is in a solution form resulting in higher rates of hypercalcemia and 2) laxative effect due to the osmotic effects of unabsorbed maltitol reaching the colon when the liquid dosage form is administered at high doses along with food products and nutritional supplements that contain high amounts of maltitol, such as Nepro® designed specifically for patients with chronic kidney failure on dialysis.

The results of the Study LP-RTG-01-01 provide assurance that the rate and extent of calcium absorption is lower compared to PhosLo™ Gelcaps and at worst it is similar. Hence the risk for hypercalcemia is expected to be no different for the two dosage forms.

The amount of maltitol for the maximum recommended dosage of Phoslyra™ (90 mL/day or 18 gms maltitol) is less than the threshold level of maltitol (30 mg) reported to produce laxative effects. Further, even with the maximum recommended dosage of Phoslyra™, a total of 6 gms maltitol is consumed with a single administration. However, maltitol is used in many food products and nutrition supplements that may be used in the end-stage renal disease population. So as to avoid exposure to high dose of maltitol, the Warning and Precautions section of the label is updated to indicate this fact.

In conclusion, the benefits of PhoslyraTM outweigh the potential risks.

- Recommendation for other Postmarketing Requirements and Commitments

A liquid formula for PhosLo ultimately may be used in the pediatric population. Therefore, a Written Request must be encouraged although PhosLo received an Orphan Drug approval letter dated December 22, 1988.

Appendix 1:

From: Pinto, Julia
Sent: Wednesday, April 28, 2010 11:49 AM
To: Madabushi, Rajnikanth; Stockbridge, Norman L
Cc: Wachter, Lori; Henry, Don
Subject: RE: (b) (4) Calcium Acetate [NDA 22-581, ANDA91-561]

Raj
You are correct. Just a further clarification (b) (4) nspection is complete, but a recommendation has not been made, because of several iss d during the inspection. Further, Lyne labs, is still a "withhold". I spoke with Coki Cruz in OC, and he is working with the district o (b) (4) resolution/recommendation for both of these facilities. Therefore, in addition to the inspection, as you discussed below, a "withhold" for either or both (b) (4) and Lyne Labs, can also mean a CR letter for this cycle pending resolution of the compliance issues.
I will keep everyone informed, as I learn more from OC.

Regards
Julia

From: Madabushi, Rajnikanth
Sent: Wednesday, April 28, 2010 11:40 AM
To: Stockbridge, Norman L
Cc: Pinto, Julia; Wachter, Lori
Subject: FW: (b) (4) Calcium Acetate [NDA 22-581, ANDA91-561]

Hi Norman,
Just talked with Julia. The situation is as below:
Looks like there was an additional site to be inspected for release testing and was not done. The sponsor was not aware that (b) (4) (b) (4) was involved with release testing. It is also not clear what aspects of the testing were done at (b) (4) The sponsor has been communicated and we are awaiting their response.

The other site Lyne Labs inspection is complete and currently on "withhold" status by Office of Compliance (OC) and a final recommendation is pending.

There are couple of scenarios how this may pan-out:
1) If the OC gives approval for Lyne Labs and if the (b) (4) was performing the same testing, then there is a possibility of waiving off the inspections and go ahead with action
2) If the (b) (4) was involved with different aspects of release testing then an inspection becomes necessary. This will result in sponsor having to submit an amendment and the inspection be performed. This will definitely result in a CR action for this cycle pending the inspection results.

Julia: Please comment if I mi-interpreted any of our conversation.
regards
Raj

From: Wachter, Lori
Sent: Monday, April 26, 2010 3:40 PM
To: Pinto, Julia
Cc: Madabushi, Rajnikanth
Subject: RE: (b) (4) Calcium Acetate [NDA 22-581, ANDA91-561]

Hi Julia,
Can you please explain to me what this e mail means? Is the inspection for (b) (4) completed? Is it acceptable?

Thanks,
~Lori

From: Pinto, Julia
Sent: Monday, April 26, 2010 9:14 AM
To: Henry, Don; Wachter, Lori
Subject: FW: (b) (4), Calcium Acetate [NDA 22-581, ANDA91-561]
Importance: High

FYI,
Shall I enter the EES?

From: Cruz, Concepcion
Sent: Sunday, April 25, 2010 12:00 PM
To: Chidambaram, Nallaperum; Pinto, Julia; Danso, Benjamin; Bykadi, Gururaj
Cc: CDER EESQUESTIONS
Subject: (b) (4) Calcium Acetate [NDA 22-581, ANDA91-561]
Importan High

All,

Recent inspection of (b) (4) revealed that (b) (4) is performing release testing for (b) (4) Calcium Acetate.

An EER should be created for:

(b) (4)

Coki Cruz, Team Leader
d: 301-796-3254
m: 240-401-6156
f: 301-847-8742

Appendix 2:

From: Wachter, Lori
Sent: Monday, April 26, 2010 10:58 AM
To: Madabushi, Rajnikanth
Subject: FW: Phoslyra (NDA 022581) Proprietary Name Review

Hi Raj,
Here is the e mail regarding the use of dual trade names from DMEPA.

Thanks,
~Lori

From: Stockbridge, Norman L
Sent: Wednesday, April 21, 2010 3:19 PM
To: Holmes, Loretta
Cc: Wachter, Lori
Subject: RE: Phoslyra (NDA 022581) Proprietary Name Review

The Division favors use of dual tradenames.
If you need a memo to file, please let us know.
Regards,
Norman

From: Holmes, Loretta
Sent: Wednesday, April 21, 2010 2:18 PM
To: Wachter, Lori
Cc: Toliver, Kristina; Ton, Phuong Nina
Subject: Phoslyra (NDA 022581) Proprietary Name Review

Hi Lori,
This is just a reminder that DMEPA is in the process of finalizing the Phoslyra proprietary name review. We find the name acceptable and are O.K. with the use of dual tradenames. **We understand the Division prefers the use of dual tradenames but we need a statement to this effect from the Division to put in our review.**
Thanks,
Loretta

Loretta Holmes, BSN, PharmD
Safety Evaluator
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Medication Error Prevention and Analysis (DMEPA)
10903 New Hampshire Avenue
Building 22, Room 4445, Mail Drop 4447
Silver Spring MD 20993 0002
Office: 301 796 0170 Fax: 301 796 9865
Email: loretta.holmes@fda.hhs.gov

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/

RAJANIKANTH MADABUSHI
04/29/2010