CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-502

Name: Eliphos Tablets [Calcium Acetate Tablets USP, 667 mg (equivalent to 169 mg Calcium)]

Sponsor: Beckloff Associates, Inc.

Approval Date: November 24, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-502

Beckloff Associates, Inc.
U.S. Agent for: Cypress Pharmaceutical, Inc.
Attention: William C. Putnam, Ph.D.
Director, Executive Consultant
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 16, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Eliphos Tablets [Calcium Acetate Tablets USP, 667 mg (equivalent to 169 mg Calcium)].

Reference is also made to your amendments dated August 8, November 30, and December 27, 2007; and June 2, November 6, and November 17, 2008.

The reference listed drug (RLD) upon which you have based your ANDA, PhosLo Tablets, 667 mg, of Fresenius Medical Care North America (Fresenius), is no longer being marketed in the United States. As a result, PhosLo Tablets were moved to the discontinued section of the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). In a Federal Register Notice issued on July 31, 2007, the agency announced its determination that PhosLo Tablets, 667 mg, were not withdrawn from sale for reasons of safety or effectiveness. This determination allows the agency to continue to approve ANDAs for the discontinued drug product.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has

determined your Eliphos Tablets [Calcium Acetate Tablets USP, 667 mg (equivalent to 169 mg Calcium)] to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, PhosLo Tablets, 667 mg (equivalent to 169 mg Calcium), of Fresenius Medical Care North America. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

For administrative purposes, please designate this submission as "***Miscellaneous Correspondence – SPL for Approved ANDA 78-502***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
11/24/2008 01:39:14 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

LABELING

b(4)

b(4)

Hawthorne Pharmaceuticals, Inc.

b(4) Eliphos™ 200ct Tablets

2.500" x 5.875"

Back

10.125"

2.500"

ELIPHOS™ Tablets
NDC 63717-910-02
Rx Only

Description: Each white, round tablet (stamped "CYP 910") contains 667 mg of calcium acetate, USP (anhydrous; $Ca(CH_3COO)_2$; MW = 158.17 grams) equal to 169 mg (8.45 mEq) calcium, polyethylene glycol 8000, NF; sodium lauryl sulfate, NF; and crospovidone, NF. ELIPHOS™ (Calcium Acetate, USP) are administered orally for the control of hyperphosphatemia in end stage renal failure.

Clinical Pharmacology: Patients with advanced renal insufficiency (creatinine clearance less than 30 mL/min) exhibit phosphate retention and some degree of hyperphosphatemia. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy, and soft-tissue calcification. The mechanism by which phosphate retention leads to hyperparathyroidism is not clearly delineated. Therapeutic efforts directed toward the control of hyperphosphatemia include reduction in the dietary intake of phosphate, inhibition of absorption of phosphate in the intestine with phosphate binders, and removal of phosphate from the body by more efficient methods of dialysis. The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient. Dialysis patients absorb 40% to 80% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced by using phosphate binders in most renal failure patients on maintenance dialysis. Calcium acetate (ELIPHOS™), when taken with meals, combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Maintenance of serum phosphorus below 6.0 mg/dl is generally considered as a clinically acceptable outcome of treatment with phosphate binders. ELIPHOS™ is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

Orally administered calcium acetate from pharmaceutical dosage forms has been demonstrated to be systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under nonfasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions.

Indications and Usage: ELIPHOS™ is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

Contraindications: Patients with hypercalcemia.

Warnings: Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with ELIPHOS™.

Progressive hypercalcemia due to overdose of ELIPHOS™ may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period.

The serum calcium times phosphate (CaXP) product should not be allowed to exceed 60. Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft-tissue calcification.

Precautions: General: Excessive dosage of ELIPHOS™ induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. ELIPHOS™ should not be given to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias. ELIPHOS™ therapy should always be started at low dose and should not be increased without careful monitoring of serum calcium. An estimate of daily dietary calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically.

Information for the patient: The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of nonprescription antacids. Patients should be informed about the symptoms of hypercalcemia (see **ADVERSE REACTIONS** section).

Drug Interactions: ELIPHOS™ may decrease the bioavailability of tetracyclines.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term animal studies have not been performed to evaluate the carcinogenic potential, mutagenicity, or effect on fertility of calcium acetate tablets.

Pregnancy: Teratogenic Effects: Category C. Animal reproduction studies have not been conducted with calcium acetate tablets. It is also not known whether calcium acetate tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Calcium acetate tablets should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and efficacy of calcium acetate tablets have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of calcium acetate tablets ($n = 91$), 25 percent were 65 and over, while 7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Adverse Reactions: In clinical studies, patients have occasionally experienced nausea during calcium acetate tablet therapy. Hypercalcemia may occur during treatment with ELIPHOS™. Mild hypercalcemia (Ca > 10.5 mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea, and vomiting. More severe hypercalcemia (Ca > 12 mg/dl) is associated with confusion, delirium, stupor, and coma. Mild hypercalcemia is easily controlled by reducing the ELIPHOS™ dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing calcium acetate tablets therapy.

Decreasing dialysate calcium concentration could reduce the incidence and severity of ELIPHOS™ induced hypercalcemia. The long-term effect of calcium acetate tablets on the progression of vascular or soft-tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent allergic reactions.

Overdosage: Administration of ELIPHOS™ in excess of the appropriate daily dosage can cause severe hypercalcemia (See **ADVERSE REACTIONS**).

Dosage and Administration: The recommended initial dose of ELIPHOS™ for the adult dialysis patient is 2 tablets with each meal. The dosage may be increased gradually to bring the serum phosphate value below 6 mg/dl, as long as hypercalcemia does not develop. Most patients require 3–4 tablets with each meal.

How Supplied: In tablet form with "CYP 910" debossed on one side and plain on the other, for oral administration. Each white round tablet contains 667 mg of calcium acetate (anhydrous $Ca(CH_3COO)_2$; MW = 158.17 grams) equal to 169 mg (8.45 mEq) calcium, polyethylene glycol 8000, NF; sodium lauryl sulfate, NF; and crospovidone, NF.

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5.000"

Page #2
(Back of Cover)

Page #3

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☐ APPROVED

☐ APPROVED WITH NOTED REVISIONS

☐ REVISE AND RE-PROOF APPROVAL SIGNATURE_____

THIS PROOF IS NOT INTENDED FOR COLOR REPRESENTATION. PLEASE REVIEW FOR COPY AND POSITIONING OF GRAPHICS AND TEXT.

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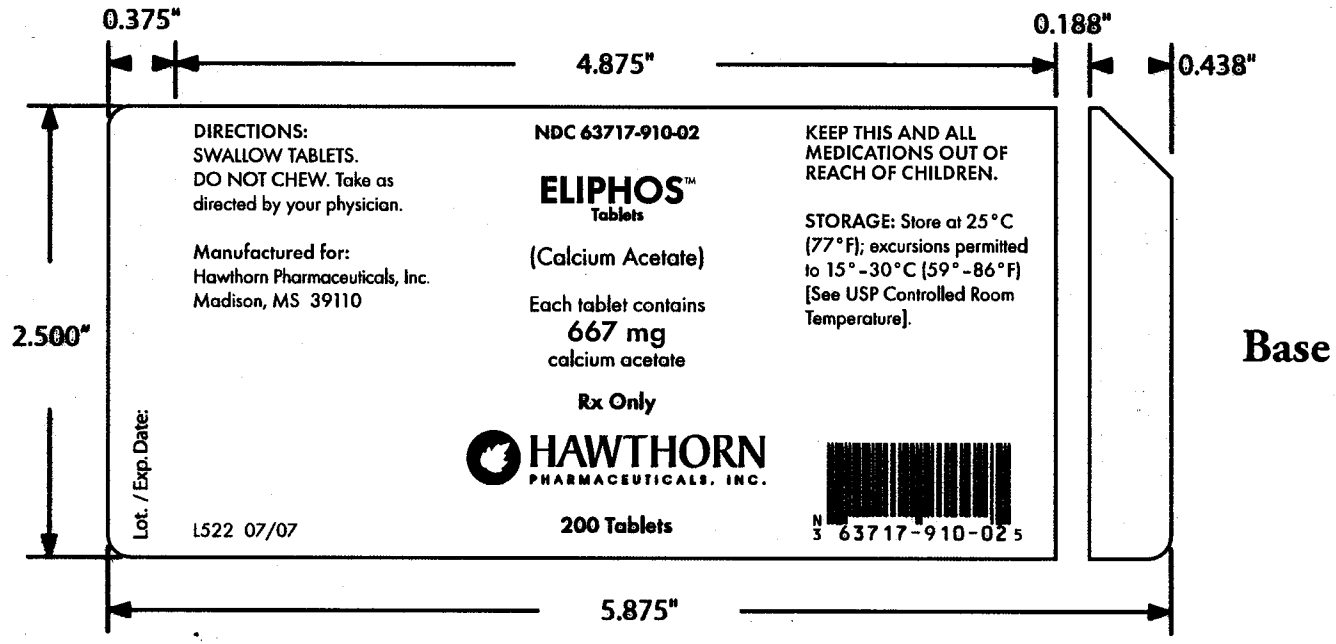
b(4)

Hawthorne Pharmaceuticals, Inc.

b(4) Eliphos™ 200ct Tablets

2.500" x 5.875"



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- ☐ APPROVED WITH NOTED REVISIONS
- ☐ REVISE AND RE-PROOF

APPROVAL SIGNATURE _____

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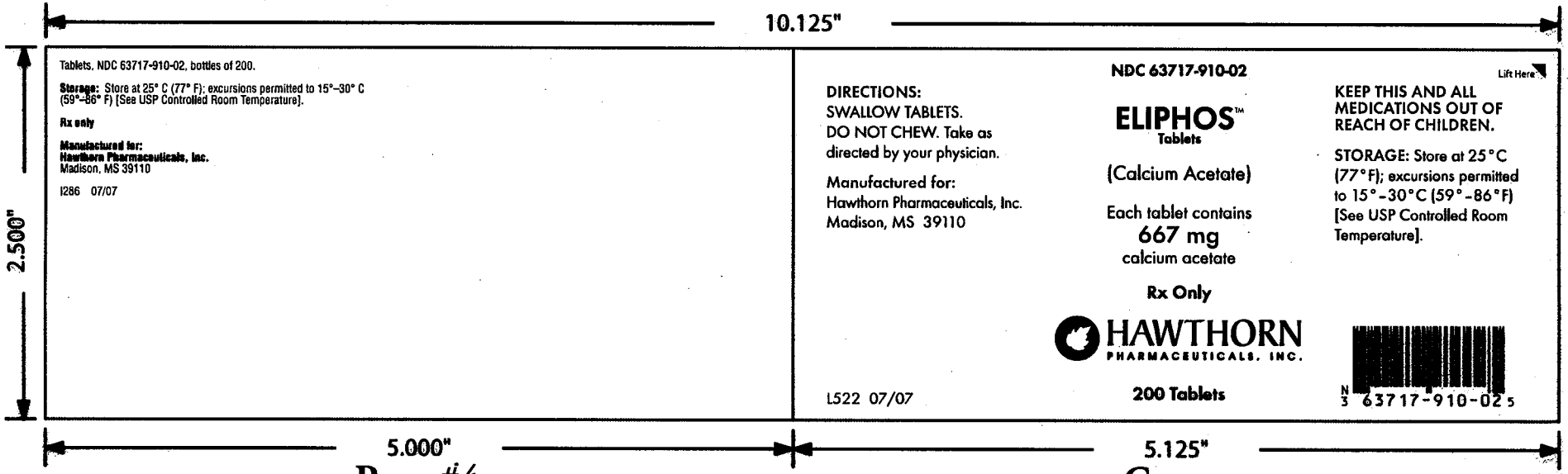
Hawthorne Pharmaceuticals, Inc.

b(4) Eliphos™ 200ct Tablets

2.500" x 5.875"

Front



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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

LABELING REVIEWS

****Proprietary name requires re-review prior to approval****

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-502

Date of Submission: August 8, 2007

Applicant's Name: Cypress Pharmaceutical, Inc.

Established Name: Calcium Acetate Tablets USP, 667 mg (EQ 169 mg calcium)

Proposed Proprietary Name: Eliphos Tablets

APPROVAL SUMMARY:

1. Do you have Final Printed Labels and Labeling? Yes.

2. CONTAINER LABEL with Fold-out PHYSICIAN INSERT (Bottles of 200s)
   Satisfactory in final print as submitted in the August 8, 2007 amendment.

3. Revisions needed post-approval: No.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: PhosLo® Tablets *This NDA is now in the discontinued section of the orange book.

NDA Number: 19-976

NDA Drug Name: Calcium Acetate Tablets

NDA Firm: Nabi Biopharmaceuticals

Date of Approval of NDA Insert and supplement: NDA 19-976/S-006; approved 2/2/04 [Revised August 2003]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES

Patent Data 19-976 (in the discontinued section of the orange book)

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4870105	APR 07,2007	U-381	TREATMENT OF HYPERPHOSPHATEMIA	PIII [Vol. A1.1, pg. 7]	None

Exclusivity Data

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

FOR THE RECORD:

1. MODEL LABELING

The reference listed drug for this product is PhosLo® Tablets (Nabi Biopharmaceuticals; NDA 19-976/S-006; approved 2/2/04 [Revised August 2003]). This NDA is now in the discontinued section of the orange book.

019976	CALCIUM ACETATE	TABLET; ORAL	EQ 169MG CALCIUM **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	PHOSLO	FRESENIUS MEDCL

USP Calcium Acetate Drug Substance Monograph:

- **Packaging and storage—** Preserve in tight containers.
- **Labeling—** Where Calcium Acetate is intended for use in hemodialysis or peritoneal dialysis, it is so labeled.

USP Calcium Acetate Drug Product monograph

- **Packaging and storage—** Preserve in well-closed containers.

2. PATENTS/EXCLUSIVITIES

Patent Data 19-976 (in the discontinued section of the orange book)

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4870105	APR 07,2007	U-381	TREATMENT OF HYPERPHOSPHATEMIA	PIII [Vol. A1.1, pg. 7]	None

Exclusivity Data

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

(b) (4)

4. CONTAINER/CLOSURE

Bottles: White, (b) (4)

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
ANDA: Calcium Acetate USP; Polyethylene Glycol 8000, Sodium Lauryl Sulfate, Crospovidone

6. PACKAGING CONFIGURATIONS

RLD: The innovator markets their product in bottles of 200.
ANDA: The applicant proposes to market in bottles of 200.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA: Store at Controlled Room Temperature, 15°-30°C.
ANDA: Store at 25°C (77°F) excursions permitted to 15o-30oC (59o-86oF)[see USP Controlled Room Temperature].

8. FINISHED PRODUCT DESCRIPTION

White to off-white round-shaped tablets (b) (4) diameter), debossed with CYP 910 on one side, plain on the other side

9. PROPOSED PROPRIETARY NAME: Review completed July 18, 2007

1. DMETS has no objections to the use of the proprietary name, Eliphos. This is considered a final decision. approval of the ANDA is delayed beyond 90 days from the signature date of this document, the name with associated labels and labeling must be re-evaluated. A re-review of the name before ANDA approval will out any objections based upon approvals of other proprietary and/or established names from the signature of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Eliphos, acceptable from a promotional perspective.
4. The Division of Cardiovascular and Renal Products has no objections to the proprietary name Eliphos.

Date of Review: November 1, 2007 Date of Submission: August 8, 2007 (amendment)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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

/s/

Ruby Wu
11/1/2007 01:08:41 PM
LABELING REVIEWER

John Grace
11/2/2007 08:14:22 AM
LABELING REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop Room 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 2007-288
February 5, 2007	June 5, 2007	
DATE OF DOCUMENT: October 16, 2006		

TO: Peter Rickman
Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-610

THROUGH: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:
Eliphos
(Calcium Acetate Tablets)
667 mg

ANDA#: 78-502

ANDA SPONSOR: Cypress Pharmaceutical, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Eliphos. This is considered a final decision. If the approval of the ANDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before ANDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Eliphos, acceptable from a promotional perspective.

4. The Division of Cardiovascular and Renal Products has no objections to the proprietary name Eliphos.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Tanya Clayton, project manager, at 301-796-0871.

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: March 8, 2007

ANDA#: 78-502

NAME OF DRUG: Eliphos (Calcium Acetate Tablets) 667 mg

ANDA HOLDER: Cypress Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Labeling and Program Support in the Office of Generic Drugs (HFD-610), for assessment of the proprietary name, Eliphos, regarding potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Eliphos is a nutritional supplement indicated for the control of hyperphosphatemia in end stage renal failure. The usual dose of Eliphos is two tablets (1334 mg) with each meal. The dosage may be increased gradually to bring the serum phosphate value below 6 mg/dL, as long as hypercalcemia does not develop. Eliphos is supplied in bottles of 200 tablets. Phoslo (NDA 21-160) is the reference listed drug. Phoslo was discontinued from the market in 2006. A Citizen's Petition was submitted by Cypress requesting that the FDA determine if the drug was withdrawn from sales due to safety or efficacy reasons. The Agency is currently drafting a response to the Citizen's Petition.

III. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Eliphos to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Eliphos. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name, Eliphos, acceptable from a promotional perspective.

2. The Expert Panel identified fifteen proprietary names that were thought to have the potential for confusion with Eliphos. They are: (b) (4) Euphrasia, Etopophos, Iloprost, Clobex, Elipten, (b) (4) Eliprim, Elspar, Lipitor, Alefos, Aliflus, (b) (4) Aluphos, and Alufos. The panel also felt the name Eliphos, sounded like it was supposed to elevate phosphate levels rather than decrease phosphate levels. Additionally, the Expert Panel suggested that names beginning with the letter 'O' should be searched.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Eliphos with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An outpatient prescription and an inpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a requisition for Eliphos (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION

VERBAL PRESCRIPTION

Outpatient Prescription:

Eliphos 667 mg.
2 tablets with each meal
UD #240

"Eliphos 667, dispense number 240. Take 2 tablets with each meal as directed."

Inpatient Prescription:

Eliphos 667 mg #tabs 2 each meal as directed

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. COMMENTS FROM THE DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
Per a March 24, 2007 e-mail, the Division of Cardiovascular and Renal Products has no objections to the name Eliphos.

D. SAFETY EVALUATOR RISK ASSESSEMEMNT

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

In reviewing the proprietary name Eliphos, 15 names were identified as having a similar sound or appearance to Eliphos. These names are (b) (4) Euphrasia, Etopophos, Iloprost, Clobex, Elipten, (b) (4) Eliprim, Elspar, Lipitor, Alefos, Aliflus, (b) (4) Aluphos, and Alufos.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Eliphos.

Initial analysis of the 15 names identified above, DMETS determined that the following twelve names: (b) (4) Euphrasia, Etopophos, Clobex, Elipten, Eliprim, Elspar, Alefos, Aliflus, (b) (4) Aluphos, and Alufos would not be considered further for the following reasons.

- In addition to lacking orthographic and or phonetic similarities with Eliphos, Euphrasia, Etopophos, Clobex, and Elspar they do not share product commonalities such as dosage form, route of administration, product strength, usual dose, and/or indication of use.
- Aliflus is a foreign product (Italy) that does not share product commonalities such as dosage form, route of administration, product strength, usual dose, and/or indication of use with Eliphos.

- Elipten (Aminoglutethimide) is a foreign product that is available in the United States under the tradename Cytadren.
- The names Alefos, Aluphos, Alufos, and Eliprim are all foreign products. The only information found on Alefos and Aluphos is contained in Micromedex, which only listed the active ingredients of each product (alendronic acid and aluminum phosphate, respectively). Alufos, available in Korea, was cited on google.com as an antacid containing aluminum phosphate and magnesium oxide. No additional information can be found on Alefos, Aluphos, and Alufor in commonly used drug references such as the Orange Book, Red Book, Facts and Comparisons, Clinical Pharmacology, etc.
- The names (b) (4) and (b) (4) were proposed names for separate products that are/were the subject new drug applications, however, neither name was used.

The remaining three names ((b) (4) Lipitor, and Ventavis) were evaluated further based on their increased potential for look-alike and sound-alike similarity and product characteristics. It was determined that none of these names pose an increased risk for name confusion with Eliphos due to lack of overlapping product characteristics such as indication of use, product strength, usual dose, route of administration, dosage form, and/or dosing frequency. These differences are noted in the last column of Table 1 on page 6.

Table 1: Names Needing Further Analysis

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**	Differing Product Characteristics
Eliphos	Calcium Acetate Tablets 667 mg	Two tablets by mouth with each meal		
[redacted]				(b) (4)
Lipitor	Atorvastatin Tablets 10 mg, 20 mg, 40 mg, 80 mg	10 mg to 80 mg by mouth once daily	LA	No Overlap • **Usual dose** ➢ Two tablets (1334 mg) vs. 10 mg to 80 mg • **Dosing Frequency** ➢ Three times daily, with meals vs. once daily • **Indication of Use** ➢ Hyperphosphatemia vs. hyperlipidemia • **Product Strength** ➢ 667 mg vs. 10 mg, 20 mg, 40 mg, and 80 mg
Ventavis	**Iloprost** Inhalation Solution 20 mcg/2 mL	2.5 mcg to 5 mcg inhaled via nebulizer six to nine times daily	LA	No Overlap • **Dosing Frequency** ➢ Three times daily, with meals vs. six to nine time daily • **Route of administration** ➢ Oral vs. Oral Inhalation • **Dosage form** ➢ Tablet vs. Inhalation Solution • **Indication of use** ➢ Hyperphosphatemia vs. Primary Pulmonary Hypertension • **Usual dose** Two tablets vs. 2.5 mcg to 5 mg

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
*****Name pending approval. Not FOI releasable.**

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and insert labeling of Eliphos, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

A. Container Label

1. The dosage form should appear in conjunction with the established name (i.e., inside or outside of the brackets). Therefore, we recommend the following presentation noted below:

Eliphos
(Calcium Acetate) Tablets
667 mg

2. Per 21 CFR 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name (see label graphic below).

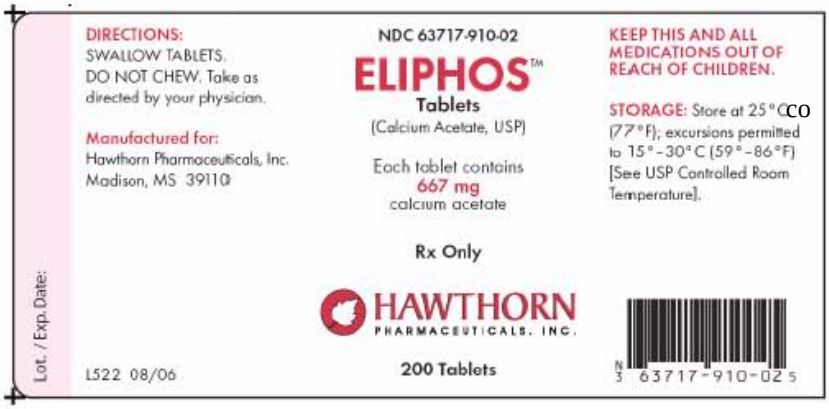
3. Increase the prominence of the product strength (see label graphic below) so that is it not confused with the net quantity.

4. Revise the "Directions" statement to read "Usual Dosage: SWALLOW TABLETS, DO NOT CHEW. See package insert."

5. Decrease the prominence of the sponsor logo. As currently presented, it is more prominent than important information such as the proprietary name, established name, product strength, and net quantity (see below).

Revise per comment A-4.

Decrease prominence per comment A-5.



Revise and increase the prominence of per comments A-1 & A-2.

Increase prominence per comment A-3.

B. Insert Labeling - No comments at this time.

Attachment 1

Outpatient Verbal	Inpatient Verbal	Verbal
Eliphos	Eliphas	Allofof
Eliphos	Eliphas	Elafof
Eliphos	eliphos	Elafof
Eliphos	Eliphos	Elafost
Eliphos	Eliphos	Elaphos
Eliphos	Eliphos	Elaphos
Eliphos	Eliphos	Elaphos
Eliphos	Eliphos	Elaphos
Eliphos	Eliphos	Elaphos
Eliphos	Eliphos	Elefas
eliphos	Eliphos	Elefos
Eliphos	Eliphos	Elefoss
Elispho	Eliphos	Elephos
	Eliphos	Elifos
	Eliphos	Ellafof
	Elisphas	Ellaphos
		Ellefof
		Elofos

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

/s/

Kristina Arnwine
7/17/2007 01:18:33 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
7/17/2007 01:44:18 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/18/2007 06:33:47 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/18/2007 07:04:19 AM
DRUG SAFETY OFFICE REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-502
Date of Submission:	October 16, 2006 (original)
Applicant's Name:	Cypress Pharmaceutical, Inc.
Established Name:	Calcium Acetate Tablets USP, 667 mg (EQ 169 mg calcium)
Proposed Proprietary Name:	Eliphos Tablets

Labeling Deficiencies:

1. GENERAL COMMENT:
   Your proposed proprietary name "Eliphos" is under review. We will inform you of our comments when they become available. Please note that in the event that your application is approved after 90 days of the current submission then the name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. CONTAINER LABEL (Bottles of 200s)
   a. Ensure that the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
   b. Increase the prominence of the expression of strength.

3. PHYSICIAN INSERT:
   How supplied: Please include the product imprinting in the description of the tablets.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

FOR THE RECORD:

1. MODEL LABELING

The reference listed drug for this product is PhosLo® Tablets (Nabi Biopharmaceuticals; NDA 19-976/S-006; approved 2/2/04 [Revised August 2003]). This NDA is now in the discontinued section of the orange book.

USP Calcium Acetate Drug Substance Monograph:

- **Packaging and storage—** Preserve in tight containers.
- **Labeling—** Where Calcium Acetate is intended for use in hemodialysis or peritoneal dialysis, it is so labeled.

USP Calcium Acetate Drug Product monograph

- **Packaging and storage—** Preserve in well-closed containers.

2. PATENTS/EXCLUSIVITIES

Patent Data 19-976

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4870105	APR 07,2007	U-381	TREATMENT OF HYPERPHOSPHATEMIA	PIII [Vol. A1.1, pg. 7]	None

Exclusivity Data

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

(b) (4)

4. CONTAINER/CLOSURE

Bottles: White, (b) (4)

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
ANDA: Calcium Acetate USP; Polyethylene Glycol 8000, Sodium Lauryl Sulfate, Crospovidone

6. PACKAGING CONFIGURATIONS

RLD: The innovator markets their product in bottles of 200.
ANDA: The applicant proposes to market in bottles of 200.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA: Store at Controlled Room Temperature, 15°-30°C.
ANDA: Store at 25°C (77°F) excursions permitted to 15o-30oC (59o-86oF)[see USP Controlled Room Temperature].

8. DISPENSING STATEMENTS COMPARISON

RLD: none
ANDA: none

9. FINISHED PRODUCT DESCRIPTION

White to off-white round-shaped tablets (b) (4) diameter), debossed with CYP 910 on one side, plain on the other side

10. PROPOSED PROPRIETARY NAME: Sent consult to DMETS 2/1/07

11. BIOAVAILABILITY/BIOEQUIVALENCE:

Pending as of June 11, 2007

Date of Review: June 13, 2007 Date of Submission: October 16, 2006 (original)

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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

/s/

Ruby Wu
6/13/2007 02:17:10 PM
LABELING REVIEWER

John Grace
6/18/2007 02:42:02 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

CHEMISTRY REVIEWS

Chemistry Assessment Section

ANDA 78-502

Calcium Acetate Tablets USP, 667 mg
(ELIPHOS ™ TABLETS)

Cypress Pharmaceutical, Inc.

Ramnarayan S. Randad
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-502

2. REVIEW #: 02

3. REVIEW DATE: January 10, November 6 and 17, 2008

4. REVIEWER: Ramnarayan S. Randad, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date
FDA acceptance to filling	10/17/06
Amendment (MC)	12/19/06
Amendment (MC)	1/11/07
Amendment (AB)	12/27/07
Amendment (AF)	8/8/2007
Amendment (AB)	6/2/2008
Original	October 16, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC) (AM)	November 30, 2007
Fax Amendment (CMC) (AA)	November 06, 2008
Fax Amendment (CMC) (MC)	November 12, 2008

7. NAME & ADDRESS OF APPLICANT:

Firm's name and address	Cypress Pharmaceutical, Inc 135 Industrial Lane Madison, MS 39110
	Contact person: Robert Lewis Director , Pharmaceutical development
Telephone	601-856-4393 or 800-856-4393
FAX	601-853-1567

US representative name and address	William C. Putnam Beckloff Associates, Inc Commerce Plaza II, Suite 300 7400 West 110th Street Overland Park, KS 66210
Telephone	913-451-3955
FAX	913-451-3846

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ELIPHOS ™ TABLETS

b) Non-Proprietary Name (USAN): Calcium Acetate Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Reference Product: PhosLo® Gelcaps, 667 mg (discontinued per orange book)
Manufacturer: Nabi Biopharmaceuticals
NDA # 21-160

Nabi Pharmaceuticals possesses one patent with regard to PhosLo Tablets NDA No. 019-976. This is a "Use" patent and has expired on April 7, 2007.

	Patent #	Expiration date	Use Code
Patent	4870105	April 7, 2007	
Exclusivity	None		

Patent Certification and Exclusivity, and Basis of ANDA submission
See review #01

Reviewer's note: PhosLo has good safety record. Nabi states that the tablets have been withdrawn to (b) (4)

OGD has following ANDA for the proposed DP in solid oral dosage forms:

Firm	ANDA #
Roxane	77-728 (Cap)
Roxane	77-693 (Tab)

10. PHARMACOL. CATEGORY: Control of hyperphosphatemia in end stage renal failure

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 667 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

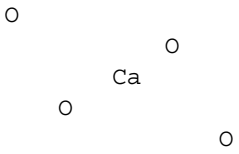
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

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

Calcium Acetate



Molecular Weight: 158.17

Molecular formula: $C_4H_6O_4 \bullet Ca$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
[redacted]			(b) (4)	1	Adequate	11/17/08	Adequate Randad Rev#5
				4	N/A		
				4	N/A		
				4	N/A		

[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

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	MQ, 3/7/08	
Methods Validation	Not submitted per OGD guidelines		
Labeling	Approval	7/3/08	MQ
Bioequivalence	Approval	7/3/08	MQ / NC
DBE-dissolution	Acceptable	7/3/08	MQ / NC
EA	N/A		
Radiopharmaceutical	N/A		

* OC withhold recommendation for [redacted] (b) (4) 16-Mar-2007

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes __X__ No If no, explain reason(s) below: MA

The Chemistry Review for ANDA 78-502

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #78-502 is approvable.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance is white crystalline powder, soluble in water, slightly soluble in methanol, and practically insoluble in ethanol, acetone, and benzene. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

- Each white, round tablet (stamped "CYP 910") contains 667 mg of calcium acetate, USP (anhydrous; $Ca(CH_3COO)_2$; MW=158.17; equal to 169 mg (8.45 mEq) calcium, polyethylene glycol 8000, NF; sodium lauryl sulfate, NF; and crospovidone, NF.

- ELIPHOS™ (Calcium Acetate, USP) are administered orally for the control of hyperphosphatemia in end stage renal failure.

- Both DS and DP have USP monograph.

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

- Calcium acetate tablets are administered orally for the control of hyperphosphatemia in end stage renal failure.

- Calcium acetate when taken with meals combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. It is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

- The (b) (4) dose for adults is 3 to 4 tablets with each meal. Thus, MDD = 667 x 12 = 8004 mg.

  Drug substance IT: (b) (4)%, QT: (b) (4)%.
  Drug product IT (b) (4)%, QT: (b) (4)%

- Each white round Calcium Acetate tablets USP are available as in bottles of 200.

- Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [See USP Controlled Room Temperature].

- The proposed expiration dating for the product is (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

III. Administrative

A. Reviewer Ramnarayan S. Randad

18 Pages of Chemistry Review have been Withheld as b4 (TS/CCI) immediately following this page

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/s/

Ramnarayan Randad
11/24/2008 07:17:21 AM
CHEMIST

Kathy P. Woodland
11/25/2008 09:12:07 AM
CHEMIST

Benjamin Danso
11/25/2008 11:01:27 AM
CSO

ANDA 78-502

Calcium Acetate Tablets USP, 667 mg
(ELIPHOS ™ TABLETS)

Cypress Pharmaceutical, Inc.

Ramnarayan S. Randad
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-502

2. REVIEW #: 01

3. REVIEW DATE: July 5, 2007; July 25, 2007

4. REVIEWER: Ramnarayan S. Randad, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date
FDA acceptance to filling	10/17/06
Amendment (MC)	12/19/06
Amendment (MC)	1/11/07

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	October 16, 2006

7. NAME & ADDRESS OF APPLICANT:

Firm's name and address	Cypress Pharmaceutical, Inc 135 Industrial Lane Madison, MS 39110
	Contact person: Robert L. Lewis Director of Product Development
Telephone	601-856-4393 or 800-856-4393 (ext.120)
FAX	601-853-1567
US representative name and address	William C Putnam Beckloff Associates, Inc Commerce Plaza II, Suite 300 7400 West 110th street Overland Park, KS 66210
Telephone	913-451-3955
FAX	913-451-3846

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ELIPHOS ™ TABLETS
(see below labeling comment)

Your proposed proprietary name "Eliphos" is under review. We will inform you of our comments when they become available. Please note that in the event that your application is approved after 90 days of the current submission then the name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

b) Non-Proprietary Name (USAN): Calcium Acetate Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Reference Product: PhosLo® Gelcaps, 667 mg (discontinued per orange book)
Manufacturer: Nabi Biopharmaceuticals
NDA # 21-160

Nabi Pharmaceuticals possesses one patent with regard to PhosLo Tablets NDA No. 019-976. This is a "Use" patent and has expired on April 7, 2007.

	Patent #	Expiration date	Use Code
Patent	4870105	April 7, 2007	
Exclusivity	None		

Patent Certification and Exclusivity, and Basis of ANDA submission
This ANDA is based upon the RLD, PhosLo Tablets (Calcium acetate), previously manufactured and marketed by Nabi Biopharmaceuticals. PhosLo Tablets are currently listed in the discontinued section of the electronic version of FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation".

PhosLo Tablet product was discontinued from the market in 2006. A Citizen Petition was submitted to FDA Dockets Management on September 27, 2006, requesting that FDA determine if the drug was withdrawn from sale due to safety or efficacy reasons. A copy of this petition is attached. The proposed drug product, ELIPHOS Tablets, manufactured by (b) (4) on behalf of Cypress, is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

Reviewer's note: PhosLo has good safety record. Nabi sates that the tablets have been withdrawn to (b) (4),

According to the FDA listed information published in the current electronic Orange Book, no exclusivity for the RLD applies.

Regarding bioequivalence studies, [redacted] (b) (4) Cypress' contract manufacturer, successfully conducted an in vitro phosphate binding study for ELIPHOS Tablets versus PhosLo Tablets.

OGD has following ANDA for the proposed DP in solid oral dosage forms:

Firm	ANDA #
Roxane	77-728 (Cap)
Roxane	77-693 (Tab)

10. PHARMACOL. CATEGORY: Control of hyperphosphatemia in end stage renal failure

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 667 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

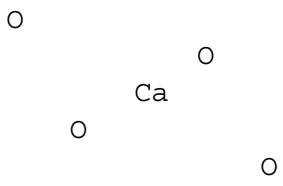
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

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

Calcium Acetate



Molecular Weight: 158.17
Molecular formula: $C_4H_6O_4 \bullet Ca$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
[redacted] (b) (4)				1	N/A	7/2/07	Inadequate Randad Rev#3
				4	N/A		
				4	N/A		
				4	N/A		

[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

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold*	MQ, 3/16/07	
Methods Validation	Not submitted per OGD guidelines		
Labeling	Deficient	6/18/07	
Bioequivalence	Pending		
DBE-dissolution	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

* OC withhold recommendation for (b) (4) 27-Feb-2007

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-502

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #78-502 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance is white crystalline powder, soluble in water, slightly soluble in methanol, and practically insoluble in ethanol, acetone, and benzene. The manufacturer of the drug substance used by the ANDA applicant is (b) (4).

- Each white, round tablet (stamped "CYP 910") contains 667 mg of calcium acetate, USP (anhydrous; $Ca(CH_3COO)_2$; MW=158.17; equal to 169 mg (8.45 mEq) calcium, polyethylene glycol 8000, NF; sodium lauryl sulfate, NF; and crospovidone, NF.

- ELIPHOS™ (Calcium Acetate, USP) are administered orally for the control of hyperphosphatemia in end stage renal failure.

- Both DS and DP have USP monograph.

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

- Calcium acetate tablets are administered orally for the control of hyperphosphatemia in end stage renal failure.

- Calcium acetate when taken with meals combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. It is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

- The [redacted] dose for adults is 3 to 4 tablets with each meal. Thus, MDD = 667 x 12 = 8004 mg.

  Drug substance IT: [redacted]%, QT: [redacted]%.
  Drug product IT: [redacted]%, QT: [redacted]%

- Each white round Calcium Acetate tablets USP are available as in bottles of 200.

- Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [See USP Controlled Room Temperature].

- The proposed expiration dating for the product is [redacted].

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable for following reasons:
1. CMC deficiencies
2. Deficient labeling review
3. Pending DBE review
4. EES withhold

III. Administrative

A. Reviewer Ramnarayan S. Randad

24 Pages of Chemistry Review have been Withheld as b4 (TS/CCI) immediately following this page

Chemistry Assessment Section

Center for Drug Evaluation and Research

cc: ANDA 78-502
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./July 25, 2007
HFD-620/Raj Bykadi, Ph.D./ Team Leader/ July 26, 2007
HFD-617/Benjamin Danso, Pharm.D./8-6-07

V:\Chemistry Division I\Team 5\Final Version For DFS\78502.CR01.NA.doc

NOT APPROVABLE

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/s/

Ramnarayan Randad
8/9/2007 09:37:55 AM
CHEMIST

Gururaj Bykadi
8/16/2007 02:53:26 PM
CHEMIST

Benjamin Danso
9/11/2007 07:31:35 AM
CSO

Gururaj Bykadi
9/11/2007 10:55:41 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-502	
Drug Product Name	Calcium Acetate Tablets USP	
Strength (s)	667 mg (eq. 169 mg Calcium)	
Applicant Name	Cypress Pharmaceutical, Inc.	
Address	135 Industrial Blvd.	
Applicant's Point of Contact	William (Trey) Putnam, Ph.D., R.A.C. Beckloff Associates, Inc. Commerce Plaza II, Suite 300 7400 West 110th Street Overland Park, KS 66210	
Contact's Phone Number	(913) 451 – 3955	
Contact's Fax Number	(913) 451 – 3846	
Previous Submission Date(s)	16 October 2006, 27 December 2007	
Submission Date(s) of Amendment(s) Under Review	02 June 2008 (Current Amendment)	
First Generic	No	
Reviewer	Johnetta L. Farrar, Ph.D.	
Study Number (s)	REP -07-195	REP-06-027
Study Type (s)	In vitro Phosphate Binding Study	In vitro Multi-pH Dissolution Study
Strength(s)	667 mg (eq. 169 mg Calcium)	667 mg (eq. 169 mg Calcium)
Waiver Request(s)	N/A	
Clinical Site	N/A	
Clinical Site Address	N/A	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	**ACCEPTABLE**	

I. EXECUTIVE SUMMARY

This is a review of a study amendment only.

In the original application, the firm submitted results of an *in vitro* phosphate binding study to establish bioequivalence (BE) between the firm's Calcium Acetate Tablets USP, 667 mg and the reference product, PhosLo® (Calcium Acetate) Tablets, 667 mg. The study was conducted using gravimetric analysis and was found to be unacceptable by the Division of Bioequivalence (DBE). However, the comparative dissolution testing using the USP method and in various pH media [0.1 N HCl, pH 4.5 Acetate Buffer, and Deionized Water using USP Apparatus II (Paddle) at a speed of 50 rpm in 900 mL of the

aforementioned medium) was found acceptable (DFS: Review-Bioequivalence Review-Biopharmaceutics-N 078502 N 000 16-Oct-2006].

In an amendment dated 27 December 2007, the firm submitted a new *in vitro* phosphate binding study with the procedure outlined in the DBE deficiency letter sent to the firm on 04 September 2007. The *in vitro* study results submitted by the firm were not fully verifiable at that time due to deficiencies in the analytical method validation. Therefore, the repeat binding study was considered incomplete at that time. In the deficiency letter dated 07 May 2008, the firm was informed of the following deficiencies:

1. Please submit raw numerical data of all standards, quality controls (QCs) and samples used in the binding study. The raw data should include peak area/height data and calculated concentration data before corrected for dilution, and also final concentration data after corrected for dilution.

2. Please summarize the standard and QC data of both calcium and phosphate from the Binding Study (REP-07-195). The summary tables should be in a similar format as in the table shown below:

	Calcium (µg/mL) Number of QCs included				Phosphate (µg/mL) Number of QCs included			
QC Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Cal. Standards Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Linearity Range (range of R^2 values)								

3. Please submit at least 20% of the chromatograms of Calcium and Phosphate analysis.

4. Please submit a list of all repeat study samples with original values and final reported values, and the reasons for reanalysis and reporting final values.

5. Please submit relevant bioanalytical standard operating procedures (SOPs).

6. Please provide the dates of the binding study and sample analysis.

The firm has submitted the current amendment to address the issues concerning the above mentioned deficiencies. The contents of the amendment includes the firm's explanation of discrepancies related to the analytical method validation as well as supplying all raw data, standard and QC summaries, chromatograms, repeat study samples, bioanalytical

SOPs, and dates of sample analysis. The firm's responses in the current amendment are acceptable. The repeat *in vitro* phosphate binding study is now considered acceptable.

The firm has previously conducted acceptable comparative dissolution testing on all strengths of its test product using the USP dissolution method, (DFS: Review-Bioequivalence Review-Biopharmaceutics-N 078502 N 000 16-Oct-2006).

> The DBE acknowledges that the firm will conduct dissolution testing using the current USP method for Calcium Acetate Tablets.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is **acceptable**.

II. TABLE OF CONTENTS

III. SUBMISSION SUMMARY

1.1 Drug Product Information[1]

Test Product	Calcium Acetate Tablets USP, 667 mg (eq. 169 mg Calcium)
Reference Product	PhosLo® Tablets, eq. 169 mg Calcium
RLD Manufacturer	Nabi Pharmaceuticals
NDA No.	19-976
RLD Approval Date	10 December 1990
Indication[2]	PhosLo is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

NOTE: PhosLo Tablets were discontinued on 29 June 2006 and withdrawn on 06 August 2007. Since the drug product was not withdrawn due to safety or efficacy reasons, it is permissible to use it as the RLD for this drug product[3]. There is currently no RLD product designated in the Orange Book for Calcium Acetate Tablets.

1.2 PK/PD Information[2,4]

Bioavailability	Calcium specific channels or carrier proteins facilitate the active transport of calcium through the intestinal cell wall. The steroid hormone 1, 25 dihydroxycholecalciferol is the major direct regulator of calcium absorption. Normal bioavailability is approximately 30% from the small intestine, which can increase up to 50% during times of increased physical demands for calcium (i.e. pregnancy or lactation). Adaption to increased demand does not occur in cases of vitamin D deficiency.
Food Effect	Orally administered calcium acetate from pharmaceutical dosage forms has been demonstrated to be systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under nonfasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions.
Tmax	Not available. Calcium levels are not determinable in blood[5].
Metabolism	Calcium is required by all body tissues. Over 99% of the body's calcium is stored in the bone, primarily as the hydroxyapatite. Constant

[1] Electronic Orange Book; http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021160&TABLE1=OB_Rx; Orange Book Data Updated through April 2008; Patent and Generic Drug Product Data Last Updated: 11 June 2008; Last accessed: 12 June 2008.
[2] DailyMed® Labeling Repository; http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6722#nlm34067-9; Search term: "calcium acetate"; Last accessed 12 June 2008.
[3] Drugs at FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails; Last accessed: 27 June 2008.
[4] Clinical Pharmacology Online; http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=88&sec=monphar; Search term: Calcium Acetate; Revision date: 06 May 2002; Last accessed: 12 June 2006.
[5] DFS: Review-Bioequivalence Review-Biopharmaceutics-N 078502 N 000 AB 27-Dec-2007.

	bone remodeling and turnover of the adult skeleton release between 250 mg to 1 gram of calcium into the systemic circulation which is then re-accumulated by the bone on a daily basis. Ninety-nine percent of filtered calcium is reabsorbed by the kidney with less than 1% excreted.
Excretion	Calcium is primarily excreted in the feces and bile. Urinary excretion plays a minor role.
Half-life	Not applicable[5].
Drug Specific Issues (if any)	Calcium combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Calcium acetate is highly soluble at neutral pH. Making the calcium readily available for binding to phosphate in the proximal small intestine. Therefore, this is a locally acting, not systemically acting, drug product.

1.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, *in vitro* phosphate binding and multiple pH dissolution profiles

1.	**Type of study:**	*In vitro* phosphate binding
	Design:	In vitro reaction of calcium in the drug product to a prepared phosphate solution, followed by a gravimetric analysis of **bound** phosphate.
	Strength:	667 mg (eq. 169 mg Calcium)
	Subjects:	N/A
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	Phosphate binding of the test product ≥ 90% that of the RLD.
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations[6]:	Recommendations taken from the review of controlled correspondence # 07–0059.

[6] Current recommendations found in the Review of Controlled Correspondence Number:07-0059 (ref controlled correspondence # 06-0794), Calcium Acetate Tablets and Gelcaps, In Vitro BE Study Protocol, 04 December 2006.

Summary of OGD or DBE History[6] (for details, see Appendix):	The DBE recommends the following alternative phosphate binding protocol designed to provide (i) phosphate binding capacity of the test and reference drug product, and (ii) phosphate binding profiles of the test and reference drug products that are useful for determination of bioequivalence of the drug product. The procedure below, describing one set of data, should be performed 12 times each for test and reference product. The study consists of the following: • Completely dissolve a tablet or capsule in an appropriate volume in vessels for test and reference separately. • In deionized water, prepare solutions with amounts of Na_3PO_4 ranging from 0.0mMoles to 5.6334 mMoles. • Add the appropriate Na_3PO_4 solution to the dissolved Calcium Acetate tables or capsules and incubate until complete precipitation has occurred. • Separate the supernatant from the precipitate using an appropriate method. • Measure the free calcium and free phosphate in the supernatant using a validated analytical method. Present the data for mMoles (or mg) of calcium and phosphate in the supernatant of the vessels. Determine the phosphate binding capacity in mMoles (or mg) using an appropriate method. Vessel data may be used to provide the phosphate binding profile. Compare the T/R binding capacity ratios. In addition, the DBE recommended the following dissolution testing: USP Apparatus II (Paddle) at 50 RPM and, USP Apparatus I (Basket) @ 100 RPM Medium: Water, 0.1 N HCl, Acetate Buffer pH 4.5, Borate Buffer pH 6.8 Volume: 900 ml Sampling time: 5, 10, 15 and 30 minutes. **Literature Review[5]:** In the Journal of Pharmaceutical and Biomedical Analysis Vol.19 pages 911-915, 1999, the authors describe an in-vitro phosphate binding assay for sevelamer. The product was incubated with mixing for 15min in phosphate solution concentrations ranging from 10-18mM that was buffered to pH 7.0 with N, N-Bis (2-hydroxyethyl)-2-aminoethanesulfonic Acid (BES).

1.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	1

1.5 Pre-Study Bioanalytical Method Validation[5] - Study Amendment (12/27/2007)

As per the review of the study amendment dated 27 December 2007, "*The analytical method validation is incomplete. The firm did not provide within-study data (including all concentrations of standards and QCs; precision, accuracy and range) for Phosphate and Calcium analyses. The firm also did not provide mean, CV%, and % accuracy data for all standard and QC concentrations as part of the pre-study assay validation for calcium and phosphate.*"

1.6 In Vitro Studies[5] – Study Amendment

1.6.1 Phosphate Binding Assay

Study Summary, In Vitro Phosphate Binding Study	
Study No.	REP-07-195
Study Design	In vitro Phosphate-Binding Study Report of Generic Calcium Acetate Tablets vs. Reference Listed Drug'
No. of units tested	2 units of test and reference, following complete dissolution and 24 hours of incubation with phosphate ions.
Test product	Calcium Acetate Tablets USP, 667 mg
Reference product	PhosLo® Tablets
Strength tested	667 mg

1.1. Calcium Acetate Tablet (Generic) Phosphate Binding Study

1.1.2. Sodium Phosphate Working Solutions Preparation

Sodium Phosphate working solutions were prepared as specified in the following table:

Level	0	1	2	3	4	5	6	7
Sodium Phosphate Tribasic (g)	0	1.07240	5.35730	10.71930	21.41870	37.46322	53.52902	107.0357
Final Volume (mL)	100	100	100	100	500	500	500	500
Concentration (mmole/mL)	0	0.02822	0.14098	0.28209	0.11273	0.19718	0.28173	0.56335

1.1.2. Phosphate Binding Time Determination

Three levels of the Phosphate Binding study were performed to determine the amount of time needed for incubation. Samples were taken at 30, 60, and 120 minutes for each level and analyzed for calcium concentration. The study results are shown in the following table:

Time Point (minutes)	Replicates	Calcium Peak Area of Phosphate Binding Samples		
		Level 1	Level 4	Level 7
30	1	11.00561	5.4450	0.0842
	2	10.5392	6.1762	0.0940
60	1	9.9909	6.1770	0.0891
	2	11.1081	6.4769	0.0644
120	1	10.7497	6.2361	0.0831
	2	11.6738	6.2383	0.0799

There was no significant difference of calcium peak area in each level of all the time points tested, which suggested that reaction between calcium and phosphate completed within 30 minutes. Since levels 1, 4 and 7 cover the entire concentration range for the phosphate binding study, the firm selected 30 minutes for the phosphate binding study for all 8 levels.

Reviewer's Note: In the pre-study method validation report, the firm provided phosphate concentration data for incubation beyond 30 minutes (120 minutes). The binding time study data showed that no additional binding occurred beyond 30 minutes of incubation.

1.1.3. Phosphate Binding for Test and RLD Products

Phosphate binding studies with 8 different phosphate concentration levels were conducted. For individual level, 12 vessels (labeled 1 to 12) were utilized. Equal amount of deionized water was added in all 12 vessels for each level (250 mL for levels 0 – 3; 240 mL for levels 4 – 7). One (1) tablet of test Calcium acetate Tablet was added to each of the vessels. After dissolution of the test calcium tablet, the freshly prepared sodium phosphate working solution for individual level was added into the corresponding vessels as specified below and incubated at 50 rpm paddle speed for 30 minutes:

Level	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Number of Vessels	12	12	12	12	12	12	12	12
Sodium Phosphate Working Solution (mL)	0	1.0	1.0	1.0	10.0	10.0	10.0	10.0
Amount of Sodium Phosphate Added (mmole)	***0***	***0.0282***	***0.1410***	***0.2821***	***1.1273***	***1.9718***	***2.8173***	***5.6335***
Amount of Water Added in each Vessel (mL)	250	250	250	250	240	240	240	240
Final Volume in Each Vessel	250	251	251	251	250	250	250	250

About 10 mL of solution was sampled after phosphate binding was completed. Samples were filtered and the filtrate analyzed for calcium and phosphate concentrations.

Calcium Amount in The Supernatant of Test Product Phosphate Binding Samples (in mg):

Sample	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6*	Level 7*
1	[redacted] (b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	179.73	172.15	171.77	160.16	103.5	46.16	0.59	0.08
Reference	0659-15	0659-16	0659-21	0659-22	0659-23	0659-29	0659-29	0659-30

*Calcium concentration of level 6 and 7 phosphate binding samples were lower than the LLOQ (5 µg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate Amount in The Supernatant of Test Product Phosphate Binding Samples (in mg):

Sample	Level 0**	Level 1**	Level 2**	Level 3**	Level 4**	Level 5**	Level 6	Level 7
1	[redacted] (b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	0.09	0.44	0.57	0.48	0.06	0.38	12.37	283.86
Reference	0659-39	0659-40	0659-40	0659-46	0659-47	0659-54	0659-55	0659-55

** Phosphate concentration of level 0 to5 phosphate binding samples were lower than the LLOQ (5 µg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate was quantitated only in two of the level 0 phosphate binding samples.

Calcium Amount in the Supernatant of RLD Phosphate Binding Samples (in mg):

Sample	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6*	Level 7*
1	[redacted] (b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	175.23	170.97	172.73	157.73	104.27	47.56	*0.74*	*0.11*

*Calcium concentration of level 6 and 7 phosphate binding samples were < LLOQ (5 mcg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate Amount in the Supernatant of RLD Phosphate Binding Samples (in mg):

Sample	Level 0*	Level 1*	Level 2*	Level 3*	Level 4*	Level 5*	Level 6	Level 7
1	[redacted] (b) (4)							
2								
3								

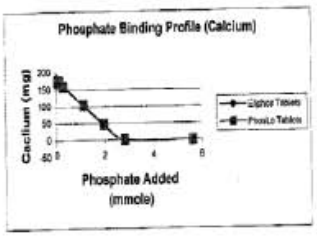
4	(b) (4)							
5								
6								
7								
8								
9								
10								
11								
12								
Average	*0*	*0.91*	*0.75*	*0.41*	*0.12*	*0.28*	9.34	286.77

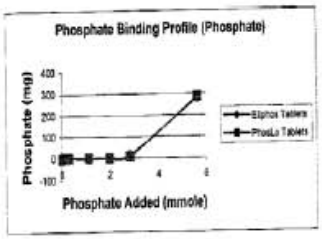
*Phosphate concentration of level 0 to 5 phosphate binding samples were < LLOQ (5 mcg/mL), so the measured results were used for information only and were not used for statistical analysis. Phosphate anion was not detected in all the level 0 phosphate binding samples.

1.1.4. DATA ANALYSIS AND REPORT

1.1.4.1.Phosphate Binding Profile

The firm generated phosphate binding profiles by plotting free Phosphate vs. Amount of Sodium Phosphate and free Calcium vs. amount of Sodium Phosphate in each vessel. The **mean** profiles for both test and reference drug products for free calcium and free phosphate are shown in the following graphs (individual profiles are in the Attachment).





1.1.4.2.Determination of Phosphate Binding Capacity

The firm calculated the difference of the free phosphate concentration in level 0 and level 7. The difference in the values obtained and the original amount of Sodium Phosphate added into level 7 is considered as the phosphate bound by calcium acetate (maximum phosphate binding capacity). Phosphate anion was not detected in most level 0 phosphate binding samples except in two test drug samples where the concentrations are far below the LLOQ. With LLOQ of 5 mcg/mL and the average concentration of Phosphate in level 7, the uncertainty of phosphate concentration in level 0 samples has < 0.5% effect on the final phosphate binding capacity determination if Phosphate concentration of level 0 samples were assumed to 0 mcg/mL. Therefore, the firm based the calculation of phosphate binding capacity on 0 mg phosphate in level 0 phosphate binding samples for both the test and RLD.

Phosphate Binding Capacity for **Test** Drug (Level 7)

Sample	Phosphate (mg) Level 7	Phosphate (mmole) Level 7	Phosphate (mmole) Added Level 7	Phosphate Binding Capacity (mmole)	Log 10 Phosphate Binding	Natural Log Phosphate Binding
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	283.86	2.9880	N/A	2.6455	0.4223	**0.9724**
SD				0.0811	0.0135	0.0311

Phosphate Binding Capacity for **Reference** Drug (Level 7)

Sample	Phosphate (mg) Level 7	Phosphate (mmole) Level 7	Phosphate (mmole) Added Level 7	Phosphate Binding Capacity (mmole)	Log 10 Phosphate Binding	Natural Log Phosphate Binding
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	286.77	3.0186	N/A	2.6149	0.4171	**0.9605**
SD				0.1054	0.0176	0.0405

Phosphate Binding Capacity for **Test** Drug (Level 6) – Compiled by Reviewer

Sample	Phosphate (mg) in Level 6	Phosphate (mg) Added Level 6	Phosphate Binding Capacity (mg)	Natural Log Phosphate Binding
1		(b) (4)		
2				
3				
4				
5				
6				
7				
8				
9				
10				

11	(b) (4)			
12				
Mean	12.62	N/A	254.94	**5.54**
SD	**1.68**		1.68	0.0066

Phosphate Binding Capacity for **Reference** Drug (Level 6) – Compiled by Reviewer

Sample	Phosphate (mg) in Level 6	Phosphate (mg) Added Level 6	Phosphate Binding Capacity (mg)	Natural Log Phosphate Binding
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	9.34	N/A	258.22	**5.55**
SD	1.85		1.85	0.0072

1.1.4.3. Statistical Analysis By Firm (Using only Level 7)

The firm calculated the 90% confidence intervals of the maximum binding capacity of the generic and RLD products.

Ln-transformed Phosphate Binding Data – Firm Calculated

	Mean	90% CI	
Test	0.9724	95.63	98.85
Reference	0.9604	93.95	98.14
T/R	**1.0124**		

Reviewer's Note:
The firm did not calculate the 90% confidence interval for the difference between formulations. The test and RLD formulations were not compared using ANOVA model with formulation as the classification variable.

b) In Vitro Results

3.6.1.1

Table 1 Calcium Amount (mg) in the Supernatant after Binding – Calculated by Reviewer.

Phosphate Spiking Level (mmoles)	LSMean (mg)		LSMean Ratio	
	Test	Reference	Point Estimate	90%CI
0 (0.0)*	179.73	175.23	1.03	100.0 – 105.3
1 (0.0282)	172.15	170.97	1.01	98.3 – 103.3
2 (0.1410)	171.77	172.70	0.99	97.3 – 101.8
3 (0.2821)	160.16	157.73	1.02	97.1 – 106.6
4 (1.1273)	103.5	104.27	0.99	96.5 – 98.7
5 (1.9718)	46.16	47.56	0.97	94.9 – 99.3
6 (2.8173)	0.00	0.00	N/A	N/A
7 (5.6335)	0.00	0.00	N/A	N/A

*Binding capacity fully demonstrated at Level 0.

Similarity Factor F2: 80.3 (calculated using mean calcium concentrations of all 6 levels)

Comments: Binding capacity of Calcium tablet = Amt of Calcium (mg) in level 0 minus Amt of Calcium (mg) in Level 7. The following acceptance conditions were satisfactory met from Level 0 to 5: 1) evaluation of binding capacity within acceptable 90% CI limits (80 – 125%); 2) point estimate within the established acceptance limit of (90 – 110%); 3) F2 > 80. Levels 6 and 7 below LLOQ and are given the value of zero.

Table 2 Phosphate Amount (mg) in the Supernatant after Binding – calculated by Reviewer.

Phosphate Spiking Level (mmoles)	LSMean (mg)		LSMean Ratio	
	Test	Reference	Point Estimate	90%CI
0 (0.0)*	0.00	0.00	N/A	N/A
1 (0.0282)	0.00	0.00	N/A	N/A
2 (0.1410)	0.00	0.00	N/A	N/A
3 (0.2821)	0.00	0.00	N/A	N/A
4 (1.1273)	0.00	0.00	N/A	N/A
5 (1.9718)	0.00	0.00	N/A	N/A
6 (2.8173)	12.37	9.34	1.37	N/A
7 (5.6335)	283.86	286.77	0.99	N/A

Similarity Factor F2: 75.19 (calculated using mean phosphate concentrations of all 2 levels)

Comments: The Phosphate concentrations in the supernatant are all zero except at the last two levels (Levels 6 and 7). The point estimate at Level 6 is outside the acceptance limit (90-110%). However, this is acceptable since the data are for supportive purpose only.

1.7 Formulation[7]

Location in appendix	Section 1.15.1, Page 22
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

1.8 *In Vitro* Dissolution[7]

Location of DBE Dissolution Review	None
Source of Method (USP, FDA or Firm)	USP
Medium	Purified Water
Volume (mL)	900 mL
USP Apparatus type	Apparatus II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolved
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

1.9 Waiver Requests[7]

Strengths for which waivers are requested	None
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

1.10 Firm's Current Responses to DBE Deficiencies

DBE's Previous Deficiency Comment No. 1 (See the review of the amendment dated 27 December 2007)**:**

Please submit raw numerical data of all standards, QCs and samples used in the binding study. The raw data should include peak area/height data and calculated concentration data before corrected for dilution, and also final concentration data after corrected for dilution.

Firm's Current Response No. 1:

"*The raw numerical data, including peak area and concentration of solution before and after correction for dilution, of all standards, QCs, and samples used in the binding study are provided by reference in Table 1.11.3-1* (see below)*.*

Included in the tables are the sample name, peak area, peak height, concentration before correction for dilution, dilution factor used in the calculation, concentration after correction for dilution, and final data (total amount in the dissolution vessel). The volume of the solution in the dissolution vessel is 250 mL.

*The ion-chromatography test samples are described as X-y-z, where X indicates either T (= Test Product; Eliphos™ Tablets, Batch CP06005) or R (= Reference Listed Drug, Phoslo® Tablets, Batch P4G114), y indicates the test level (0 to 7), and z indicates the tablet number (1 to 12). For example, sample T-1-1 indicates that it is an ion chromatography sample for Tablet Number 1 of the test product obtained from the Level 1 dissolution vessel.****"***

Table 1.11.3-1.	**Table Reference for Calcium and Phosphate Binding Study Data**
Reference	**Description**
Table 1.11.3-2	Calcium Concentration Measurement for Levels 0 and 1
Table 1.11.3-3	Calcium Concentration Measurement for Levels 2, 3, and 4
Table 1.11.3-4	Calcium Concentration Measurement for Levels 5, 6, and 7
Table 1.11.3-5	Phosphate Concentration Measurement for Levels 0, 1, and 2
Table 1.11.3-6	Phosphate Concentration Measurement for Levels 3 and 4
Table 1.11.3-7	Phosphate Concentration Measurement for Levels 5, 6, and 7

Reviewer's Comment:

The firm has provided raw numerical data of all standards, QCs and samples in the requested format. Please see the tables located in the Appendix of the review (1.15.2 Additional Attachments). The data, as submitted, is acceptable. The firm's response to deficiency comment No. 1 is **acceptable**.

DBE's Previous Deficiency Comment No. 2 (See the review of the amendment dated 27 December 2007):

Please summarize the standard and QC data of both calcium and phosphate from the Binding Study (REP-07-195). The summary tables should be in a similar format as in the table shown below:

	Calcium (µg/mL) Number of QCs included				Phosphate (µg/mL) Number of QCs included			
QC Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Cal. Standards Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Linearity Range (range of R^2 values)								

Firm's Current Response No. 2:

"*The summary of the standard and QC data from the binding study Report REP-07-195 is provided in Table 1.11.3-8 for calcium and Table 1.11.3-9 for phosphate. The binding study Report REP-07-195 was submitted in amendment SN 0004 (anda078502\0004\m5\53-clinstud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-rep-07-195\ study-rep- 07-195.pdf).****"***

Table 1.11.3-8. Standard and QC Data for Calcium							
Number of QCs Included	**14**						
Date of Analysis	11/29/2007–12/01/2007						
QC Conc. (µg/mL)	5	25	40	70			
Interday Precision (%CV)	1.99%	0.94%	0.86%	1.29%			
Interday Accuracy (%)	96.2%	100.1%	100.4%	101.0%			
Calibration Standards Conc. (µg/mL)	**5**	**25**	**30**	**40**	**50**	**60**	**70**
Interday Precision (%CV)	4.92%	0.89%	0.66%	0.26%	0.26%	0.15%	0.31%
Interday Accuracy (%)	95.9%	100.2%	100.0%	100.1%	100.2%	99.7%	99.8%
Linearity Range (Range of R^2 Values)	0.9999 to 1.0000						

Table 1.11.3-9. Standard and QC Data for Phosphate						
Number of QCs Included	**15**					
Date of Analysis	12/04/2007–12/07/2007					
QC Conc. (µg/mL)	5		30		50	
Interday Precision (%CV)	1.83%		1.33%		0.89%	
Interday Accuracy (%)	101.8%		98.5%		101.4%	
Calibration Standards Conc. (µg/mL)	**5**	**10**	**20**	**30**	**40**	**50**
Interday Precision (%CV)	0.99%	0.25%	0.42%	0.99%	0.23%	0.25%
Interday Accuracy (%)	101.7%	99.1%	97.2%	98.5%	99.0%	101.9%
Linearity Range (Range of R^2 Values)	0.9994 to 1.0000					

Reviewer's Comment:

The firm provided summary tables for the standards and QC data of both calcium and phosphate from its binding study (REP-07-195). The data, as submitted, is acceptable. The firm's response to deficiency comment No. 2 is **acceptable**.

DBE's Previous Deficiency Comment No. 3 (See the review of the amendment dated 27 December 2007):

Please submit at least 20% of the chromatograms of Calcium and Phosphate analysis.

Firm's Current Response No. 3:

"*The representative chromatograms provided for the calcium and phosphate analysis are referenced in Table 1.11.3-10. Chromatograms for 2 tablets from each study level and binding-study material (test product, RLD, or standard) are provided.****"***

Table 1.11.3-10. Representative Chromatograms for Calcium and Phosphate Analysis	
Material	**Chromatograms Provided**
Standard, Calcium Test Samples	Chromatograms are provided for each standard solution (duplicate injections): 0, 5, 25, 30, 40, 50, 60, and 70 ppm, for a total of 16 chromatograms.
Test Product, Calcium Test Samples	Chromatograms are provided for 2 tablets each from each dissolution level (0 to 7) for a total of 16 chromatograms. Samples are identified by sample name on the upper left corner of the chromatogram. The sample designation is the same as described in Response 1.
RLD, Calcium Test Samples	Chromatograms are provided for 2 tablets each from each dissolution level (0 to 7) for a total of 16 chromatograms. Samples are identified by sample name on the upper left corner of the chromatogram. The sample designation is the same as described in Response 1.
Standard, Phosphate Test Samples	Chromatograms are provided for each standard solution (duplicate injections): 0, 5, 10, 20, 30, 40, and 50 ppm, for a total of 14 chromatograms.

Table 1.11.3-10. Representative Chromatograms for Calcium and Phosphate Analysis	
Material	**Chromatograms Provided**
Test Product, Phosphate Test Samples	Chromatograms are provided for 2 tablets each from each dissolution level (0 to 7) for a total of 16 chromatograms. Samples are identified by sample name on the upper left corner of the chromatogram. The sample designation is the same as described in Response 1.
RLD, Phosphate Test Samples	Chromatograms are provided for 2 tablets each from each dissolution level (0 to 7) for a total of 16 chromatograms. Samples are identified by sample name on the upper left corner of the chromatogram. The sample designation is the same as described in Response 1.

Reviewer's Comment:

The firm has submitted at least 20% of the chromatograms for its *in vitro* phosphate binding study. The chromatograms contain no interfering peaks. The chromatograms were serially selected. Therefore, the firm's response to this deficiency comment No. 3 is **acceptable**.

DBE's Previous Deficiency Comment No. 4 (See the review of the amendment dated 27 December 2007)**:**

Please submit a list of all repeat study samples with original values and final reported values, and the reasons for reanalysis and reporting final values.

Firm's Current Response No. 4:

"*A list of all repeat-study samples and the reasons for the reanalysis are provided in Table 1.11.3-11. There were two events of repeat analysis during the testing of the phosphate-binding study. Both events were attributable to technical problems with column performance and unsuitable dilution rate of the supernatant solutions. Values obtained from the repeat analysis were included in the binding Study REP-07-195 (anda-078502\0004\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-studrep\ study-rep-07-195\ study-rep-07-195.pdf).****"***

Table 1.11.3-11. Repeat Analysis for Binding Study Samples	
Repeat Analysis 1	
Study Samples Original Values	Levels 0, 1, and 2 for Phosphate. Not available (sequence was not finished).
Reported Values	Values obtained from the reanalysis were reported in Report REP-07-195. Raw data for these analyses are provided in *Table 1.11.3-2* and *Table 1.11.3-3*.
Reasons for Reanalysis	Levels 0, 1, and 2 samples (both test product and RLD) were analyzed for phosphate concentration on 12/03/2007. System suitability was found to have failed during the analysis and the sequence was then stopped. Per (b) (4) SOP, the sequence was invalidated due to the failing system suitability and all the data generated from this sequence was not processed. Possible reason for failing of system suitability was that the column was not well-equilibrated. Samples were reanalyzed on 12/04/2007 and reanalysis results were reported in Report REP-07-195. At the time of the reanalysis, the samples were within the stability time limit of 7 days.

Table 1.11.3-11. Repeat Analysis for Binding Study Samples	
Repeat Analysis 2	
Study Samples	Level 6 for Phosphate.
Original Values	Not calculated.
Reported Values	Results from the 5 times dilution were reported in Report REP-07-195. Raw data for these samples are provided in *Table 1.11.3-7*. The samples are identified as R-6-1-5D to R-6-12-5D or T-6-1-5D to T-6-12-5D.
Reasons for Reanalysis	Level 6 supernatant samples (both test product and RLD) were originally diluted 10 times. It was found out that the phosphate concentrations in the diluted samples were lower than 5 µg/mL, which was the LLOQ of this method. Data generated from these samples was processed but no further calculation was performed. The supernatant samples were subsequently diluted 5 times in order to achieve greater accuracy of the response. The results obtained from these samples were reported in Report REP-07-195.

Reviewer's Comment:

The firm submitted a list of the repeated study samples (2) with original values and final reported values, and the reasons for reanalysis and reporting final values. Per the firm, study samples at levels 0, 1, and 2 for Phosphate were not available in the original run (sequence did not finish). *"Levels 0, 1, and 2 samples (both test product and RLD) were analyzed for phosphate concentration on 12/03/2007. System suitability was found to have failed during the analysis and the sequence was then stopped. Per* (b) (4) *, SOP, the sequence was invalidated due to the failing system suitability and all the data generated from this sequence was not processed. Possible reason for failing of system suitability was that the column was not well-equilibrated. Samples were reanalyzed on 12/04/2007 and reanalysis results were reported in Report REP-07-195. At the time of the reanalysis, the samples were within the stability time limit of 7 days."*

The firm also conducted reanalysis for study sample level 6 for Phosphate. The original values were not calculated. Per the firm, "*Level 6 supernatant samples (both test product and RLD) were originally diluted 10 times. It was found out that the phosphate concentrations in the diluted samples were lower than 5 µg/mL, which was the LLOQ of this method. Data generated from these samples was processed but no further calculation was performed. The supernatant samples were subsequently diluted 5 times in order to achieve greater accuracy of the response. The results obtained from these samples were reported in Report REP-07-195."*

The use of repeated values did not affect the outcome of the study.

The firm's response to deficiency comment No. 4 is **acceptable**.

DBE's Previous Deficiency Comment No. 5 (See the review of the amendment dated 27 December 2007)**:**

Please submit relevant bioanalytical SOPs.

Firm's Current Responses to No. 5:

"The in vitro bioequivalency tests were performed by (b) (4) *is a contract manufacturer providing typical chemical analysis on drug substances or drug products. The list of laboratory SOPs is provided.* (b) (4) *does not perform bioanalytical analyses. Relevant SOPs pertaining to the general good laboratory practices and handling of analytical data are provided (SOP 0250.001.2 and SOP 0250.005.5, respectively)***".**

Reviewer's Comment:

The firm submitted a list of laboratory SOPs as well as SOP # 0250.001.2 (Laboratory Policies and Procedures, effective: 20 December 2004) and SOP # 0250.005.5 (Handling Out-of-Specification Results, effective: 06 April 2007). The SOPs listed above are those

required for this study. As a result, the firm's response to deficiency comment No. 5 is **acceptable**.

DBE's Previous Deficiency Comment No. 6 (See the review of the amendment dated 27 December 2007)**:**

Please provide the dates of the binding study and sample analysis.

Firm's Current Responses to No. 6:

"The dates of the binding study and sample analyses are provided in Table 1.11.3-12 for calcium and Table 1.11.3-13 for phosphate."

Table 1.11.3-12. Dates of Binding Study and Sample Analysis for Calcium

Level	Binding Study Date	Sample Analysis Date	Time Difference	Solution Stability
0	11/28/2007	11/29//2007	1 day	2 days for 5 µg/mL samples and 4 days for other samples
1	11/28/2007	11/29/2007	1 day	
2	11/29/2007	11/30/2007	1 day	
3	11/29/2007	11/30/2007	1 day	
4	11/29/2007	11/30/2007	1 day	
5	11/30/2007	12/01/2007	1 day	
6	11/30/2007	12/01/2007	1 day	
7	11/30/2007	12/01/2007	1 day	

Table 1.11.3-13. Dates of Binding Study and Sample Analysis for Phosphate

Level	Binding Study Date	Sample Analysis Date	Time Difference	Solution Stability
0	11/28/2007	12/04/2007	6 days	7 days for all samples
1	11/28/2007	12/05/2007	7 days	
2	11/29/2007	12/05/2007	6 days	
3	11/29/2007	12/06/2007	7 days	
4	11/29/2007	12/06/2007	7 days	
5	11/30/2007	12/07/2007	7 days	
6	11/30/2007	12/07/2007	7 days	
7	11/30/2007	12/07/2007	7 days	

Reviewer's Comment:

The firm submitted the dates in which the *in vitro* phosphate binding study and sample analysis were performed. The SOPs were effective prior to the initiation of these studies. Therefore, the firm's response to deficiency comment No. 6 is **acceptable**.

1.11 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

V. RECOMMENDATIONS

1. The **repeat** *in vitro* phosphate binding BE study (REP -07-195) conducted by Cypress Pharmaceutical on its Calcium Acetate Tablets USP, 667 mg, comparing it with the reference product, Nabi's PhosLo® (calcium acetate) Tablets, 667 mg, is **acceptable**.

2. The firm's *in vitro* dissolution testing is **acceptable**. The dissolution testing should be conducted according to the current USP monograph for Calcium Acetate Tablets.

3. The Division of Bioequivalence deems the test product Calcium Acetate Tablets USP, manufactured by Cypress Pharmaceuticals, Inc., to be bioequivalent to the reference product, PhosLo® (calcium acetate) Tablets, 667 mg, manufactured by Nabi Pharmaceuticals.

1.12 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

VI. APPENDIX

1.13 Formulation Data[5]

Table 2.3.P.1-3. Unit Composition of ELIPHOS Tablets				
Compound	Reference to Quality Standard	Function	Quantity per Unit (mg/tablet)	Quantity per Unit (% w/w)
Calcium Acetate	*USP*	Drug substance	[redacted]	(b) (4)
Polyethylene Glycol 8000	*NF*	[redacted]	[redacted]	(b) (4)
Sodium Lauryl Sulfate	*NF*			
Crospovidone	*NF*			
Total Tablet Weight			(b) (4)	100.0
[a] = Equivalent to 667 mg on anhydrous basis (assuming water content of [redacted] w/w)				

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Inactive ingredients are within IIG limits

Comments on the drug product formulation: The formulation is acceptable.

1.14 Dissolution Data[5]

Dissolution Conditions	**Apparatus:**	Paddle
	Speed of Rotation:	50 rpm
	Medium:	Multiple Media (0.1 N HCl, pH 4.5 Acetate Buffer, Deionized Water)
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	NLT (b) (4), (Q) in 30 minutes.	

A study was conducted to compare the dissolution profile of the proposed drug product to that of the RLD. For this purpose, dissolution tests according to the *USP* specification were performed in three different pH media for both the RLD and the proposed drug product. Results of this study are summarized below:

Medium	**DI Water**	
	Calcium Acetate Tablets	**PhosLo®**
Tablets	**% Release at 15 minutes**	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	100
Range	100-101%	95-104%

Medium	0.1 N HCl	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	101
Range	100-101%	98 – 104%

Medium	pH 4.5 Acetate Buffer	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	100	102
Range	93-104%	99-105%

Comments on the dissolution: The dissolution, according to the USP method for Calcium Acetate Tablets, is **acceptable**.

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1.14.2 Additional Attachments[8] - Standard Operating Procedures (SOPs)

REVIEWED BY QA
QA: VL
DATE: 01/11/2008

(b) (4)

SOP Numbers	Title	Rev.	Effective Date
0250.001	Laboratory Policies and Procedures	2	12/20/2004
0250.002	Documenting into Laboratory Notebooks	2	11/19/2004
0250.003	Review of Laboratory Notebook	2	11/19/2004
0250.004	Preventive Maintenance of Analytical Instruments	2	11/19/2004
0250.005	Handling Out-Of-Specification Results	5	4/6/2007
0250.010	UV-VIS Spectrophotometer Suitability Check	4	6/29/2005
0250.011	Dissolution Apparatus Suitability Check	8	7/18/2007
0250.012	Laboratory Safety	3	1/10/2008
0250.014	General Guidelines on Potency Determination of In-House Reference Standards	2	11/19/2004
0250.015	Laboratory Solutions	2	12/9/2004
0250.016	Suitability Check of Temperature-Controlled Equipment	3	7/26/2005
0250.017	Suitability Check of Laboratory Balances	3	12/17/2004
0250.018	General Guidelines on Dissolution Testing	2	11/19/2004
0250.019	General Guidelines on HPLC Operation	2	11/16/2007
0250.020	Gas Chromatograph Calibration and Maintenance	5	4/25/2007
0250.021	Calibration of Thermo Separation Products HPLC System	4	1/31/2006
0250.024	Operating Procedure for Laser Particle Counter	2	5/19/2005
0250.025	Melting Point Instrument Calibration and Operation	2	1/6/2005
0250.026	Airborne Non-Viable and Viable Particulate Monitoring in the Clean Areas	5	10/12/2007
0250.027	Operation & Calibration of the Biotest RCS Air Sampler	2	1/13/2005
0250.028	Operation and Calibration of Polarimeter	3	9/19/2005
0250.030	Sample Handling, Monitoring and Reporting in Stability	6	4/26/2004
0250.033	Calibration and Maintenance of the Stability Chamber	5	4/5/2007
0250.034	Operation and Maintenance of the Stability Chamber	3	6/18/2007
0250.036	Calibration of Dickson Temperature/Humidity Data Logger Model TR320	2	4/12/2006
0250.037	Operation and Calibration of Infrared Spectrophotometer	1	4/26/2005
0250.038	Calibration of Hardness Tester and Thickness Gauge	3	9/1/2005
0250.039	Calibration and Maintenance of (b) (4)	1	1/30/2006
0250.040	Calibration and Maintenance of Disintegrator	1	1/31/2006
0250.041	Procedure of Laboratory Glassware Cleaning	3	5/20/2005
0250.042	Operation, Calibration, and Maintenance of the Automatic Dilutor	1	9/19/2005
0250.043	Operation of Waters HPLC and Empower Software	1	9/8/2005
0250.044	Assigning and Numbering Laboratory Worksheets	1	1/13/2005
0250.045	General Guidelines on Validation of Analytical Calculation Spreadsheets	0	3/3/2004
0250.046	Operation and Calibration of Density Meter	0	7/26/2004
0250.047	Calibration Procedure of Torque Tester	0	8/2/2004
0250.048	Operating and Calibration Procedure for Micropipette	0	8/2/2004
0250.049	Writing Standard Testing Methods (STM)	2	4/23/2007
0250.050	Operation and Maintenance of Varian VK Dissolution System	0	7/22/2005
0250.052	Waters HPLC System Calibration and Maintenance	0	1/31/2006
0250.053	Operation and Maintenance of EBI 2-TH 611 Humidity-Temperature Datalogger with EBI WINLOG 2000	1	8/28/2006
0250.054	Operation and Maintenance of Distek Dissolution System	0	6/13/2007
	Other Department SOPs Issued		
0200.047	Procedures for Dispensing, Sampling, and Storage Purified Water, USP	2	4/24/2007
0600.013	Procedure for Monitoring Manufacturing Areas	5	6/8/2005

[8]Tables found in an Internal Database; Electronic Document Room (EDR); Application: N078502; Document: 3962803; Location: \\CDSESUB1\EVSPROD\ANDA078502\0005; Last accessed 13 June 2008.

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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	78-502
APPLICANT:	Cypress Pharmaceutical, Inc.
DRUG PRODUCT:	Calcium Acetate Tablets USP, 667 mg (eq. 169 mg Calcium)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Your dissolution testing using the USP method is acceptable. We acknowledge that you will conduct dissolution testing using the current USP monograph for Calcium Acetate Tablets. The dissolution method is as follows:

Medium:	Purified Water
Volume:	900 mL
USP Apparatus:	Type II (Paddle)
Rotation (rpm):	50 rpm

The test product should meet the following specification:

Not less than (b)(4)% of the labeled amount of calcium acetate should be dissolved in 30 minutes from the dosage form.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME PAGE

ANDA: 78-502

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5743	6/2/2008	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Johnetta Farrar
7/1/2008 08:36:04 AM
BIOPHARMACEUTICS

April Braddy
7/1/2008 08:53:00 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
7/2/2008 10:17:48 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-502	
Drug Product Name	Calcium Acetate Tablets USP, 667mg	
Strength(s)	EQ 169mg Calcium	
Applicant Name	Cypress Pharmaceutical Inc.	
Address	135 Industrial Blvd, Madison, MS 39110	
Applicant's Point of Contact	Robert L. Lewis	
Contact's Telephone Number	(800) 856-4393	
Contact's Fax Number	(601) 853-1567	
Original Submission Date(s)	October 16, 2006	
Submission Date(s) of Amendment(s) Under Review	December 27, 2007	
Reviewer	Patrick Nwakama, Pharm.D.	
Study Number (s)	REP-07-195	REP-06-027
Study Type (s)	In vitro Phosphate Binding Study	In vitro multi-pH Dissolution Study
Strength (s)	667 mg	667 mg
Clinical Site	N/A	
Clinical Site Address	N/A	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
OUTCOME	Incomplete	

1 EXECUTIVE SUMMARY

This is a study amendment. In the original application, the firm submitted results of *in vitro* phosphate binding study conducted using gravimetric analysis that was found unacceptable by the DBE. The comparative dissolution testing using the USP method and in various pH media was found acceptable.

In the current amendment, the firm submitted a *repeat in vitro* phosphate binding study with the procedure outlined in DBE deficiency letter. The in vitro results submitted by the firm are not fully verified at this time due to deficiencies in the analytical method validation (see Deficiency Comments). The repeat binding study is considered incomplete at this time.

The application is **incomplete.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Calcium Acetate Tablets USP, 667mg
Reference Product	PhosLo® Tablets
RLD Manufacturer	Nabi Biopharmaceuticals
NDA No.	19-976
RLD Approval Date	December 10, 1990
Indication	Management of hyperphosphatemia in end stage renal failure

3.2 PK/PD Information

Bioavailability	Not applicable. The product acts by binding locally in the GI tract with phosphate present in ingested food.
Food Effect	This product's mode of action is through removing phosphate from food the subject ingests, and is, therefore, subject to oral food effects.
Tmax	Not Available. Calcium levels not determinable in blood.
Metabolism	Not applicable
Excretion	Calcium acetate is excreted in the form of calcium phosphate in the feces and as calcium in the urine.
Half-life	Not applicable.
Drug Specific Issues (if any)	It combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Calcium acetate is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine. Therefore, this is a locally acting, not systemically acting, drug product.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, in vitro phosphate binding and multiple pH dissolution profiles

1.	**Type of study:**	in vitro phosphate binding
	Design:	In vitro reaction of calcium in the drug product to a prepared phosphate solution, followed by gravimetric analysis of **bound** phosphate.
	Strength:	667 mg
	Subjects:	N/A
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	Phosphate binding of the test product $\geq$ 90% that of the RLD
Waiver request of in-vivo testing:	N/A

Source of most recent recommendations:	OGD #06-1117; [redacted] (b) (4); 10/25/06
Summary of OGD or DBE History (for details, see Appendix 4.4):	The DBE recommends the following alternative phosphate binding protocol designed to provide (i) phosphate binding capacity of the test and reference drug product, and (ii) phosphate binding profiles of the test and reference drug products that are useful for determination of bioequivalence of the drug product. The procedure below, describing one set of data, should be performed 12 times each for test and reference product. The study consists of the following: • Completely dissolve a tablet or capsule in an appropriate volume in vessels for test and reference separately. • In deionized water, prepare solutions with amounts of Na_3PO_4 ranging from 0.0 mMoles to 5.6334 mMoles. • Add the appropriate Na_3PO_4 solution to the dissolved Calcium Acetate tables or capsules and incubate until complete precipitation has occurred. • Separate the supernatant from the precipitate using an appropriate method. • Measure the free calcium and free phosphate in the supernatant using a validated analytical method. Present the data for mMoles (or mg) of calcium and phosphate in the supernatant of the vessels. Determine the phosphate binding capacity in mMoles (or mg) using an appropriate method. Vessel data may be used to provide the phosphate binding profile. Compare the T/R binding capacity ratios. In addition, the DBE recommended the following dissolution testing: USP Apparatus II (Paddle) at 50 RPM and USP Apparatus I (Basket) @ 100 RPM Medium: water, 0.1 N HCl, acetate buffer pH 4.5, borate buffer pH 6.8 Volume: 900 ml Sampling time: 5, 10, 15 and 30 minutes. **Literature Review:** In the Journal of Pharmaceutical and Biomedical Analysis Vol.19 pages 911-915, 1999, the authors describe an in-vitro phosphate binding assay for sevelamer. The product was incubated with mixing for 15min in phosphate solution concentrations ranging from 10-18mM that was buffered to pH7.0 with BES.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0

In vitro dissolution	No	1
Waiver requests	No	0
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.5 Review of Submission

(Response to DBE Deficiency Letter dated September 4, 2007)

DBE DEFICIENCY COMMENT #1

Your phosphate binding study procedure is not acceptable, because it is not designed for the determination of the phosphate precipitation capacity. You determined relative phosphate binding capacity (test/reference) by measuring the amount of calcium phosphate precipitate by gravimetric analysis and not by analyzing the free calcium and free phosphate in the supernatant once precipitation has occurred. In addition, your experiment was conducted using only one concentration of phosphate solution at one time point. To demonstrate bioequivalence using in vitro phosphate-binding capacity of the drug products (test vs. reference), you need to conduct an equilibrium experiment on the drug products that uses several concentrations (e.g., 0 to 5.6334 mMoles or higher) of phosphate solution at one incubation time point as described below.

FIRM's RESPONSE:
The firm has acknowledged the deficiency stated above.

REVIEWER'S COMMENT:
The firm has conducted an equilibrium experiment on the test and RLD products using several concentrations (e.g., 0 to 5.6334 mMoles or higher) of phosphate solution at one incubation time point as described below.

DEFICIENCY COMMENT #2

*Please repeat your in vitro phosphate binding study as **outlined** below:*

a. *Prepare eight vessels for test and eight vessels for reference. Completely dissolve one calcium acetate tablet or capsule in appropriate volume of deionized water.*
b. *Add varying amounts of sodium phosphate (Na_3PO4) in the eight incubation vessels (e.g., 0.0, 0.02817, 0.14084, 0.28167, 1.12668, 1.97169, 2.8167 and 5.6334 mMoles). Please note higher than 5.6334 mMoles of sodium phosphate may be necessary to achieve complete phosphate precipitation capacity and a meaningful phosphate binding profile. Accordingly, more than 8 vessels for test and reference will be required.*
c. *Incubate at 37°C in a shaking water bath until complete precipitation has occurred.*
d. *Separate the supernatant using appropriate method, e.g., centrifugation or vacuum filtration.*

e. *Measure the free calcium and free phosphate in the supernatant using validated analytical methods.*
f. *Carry out the binding assay (steps a-e) on 12 replicates each for test and reference products.*
g. *Present the data (mMole or mg) for calcium and phosphate (PO_4) in the supernatant in table format.*
h. *The phosphate binding capacity (maximum binding) is determined from the mMoles (or mg) difference between Vessel 1 and Vessel 8 or more as the case may be).*
i. *A plot of data from Vessels 1 through 8 (or more as the case may be) will provide the phosphate binding profile.*
j. *Compare the mean of maximum binding for test to the mean of maximum binding for reference (T/R binding ratios). For binding capacity, the T/R ratio should fall within ±10% (0.9 to 1.1). Please also provide a 90% confidence interval (transferred and log-transformed data) of the maximum binding capacity of the test and reference. The DBE will set an interim specification upon review of the submitted results. The similarity factor (f2) may be used to compare the mean profiles for the test and reference products.*

FIRM's RESPONSE:
The comparative binding studies were repeated according to DBE's outline (see full report in Section 3.6). The protocol and results for the studies are provided in Protocol PCL-07-080 ('In vitro Phosphate-Binding Study of Generic Calcium Acetate Tablets vs. Reference Listed Drug') and Report REP-07-195 ('In vitro Phosphate-Binding Study Report of Generic Calcium Acetate Tablets vs. Reference Listed Drug').

REVIEWER'S COMMENT:
The data submitted by the firm is incomplete.

DEFICIENCY COMMENT #3
Please develop sensitive, specific and validated analytical methods for measuring phosphate and calcium. Please provide pre-study and during study data (including all concentrations of standards and QCs; precision, accuracy and range) for Phosphate and Calcium analyses. Please provide bio-batch size and content uniformity for the test product. Please refer to the FDA guidance, Bioanalytical Method Validation (Issued 5/2001) for more information.

FIRM's RESPONSE:
The protocols and results for the analytical method validation for phosphate and calcium are provided in two protocols [PCL-07-094 ('Analytical Method Validation Protocol for Determination of Phosphate Anion Concentration for Calcium Acetate Tablets in vitro Phosphate Binding Study') and PCL-07-093 ('Analytical Method Validation Protocol for Determination of Calcium Cation Concentration for Calcium Acetate Tablets in vitro Phosphate Binding Study')] and two reports [REP-07-197 ('Analytical Method Validation Report for Determination of Phosphate Anion Concentration for Calcium Acetate Tablets In-Vitro Phosphate Binding Study') and REP-07-196 ('Analytical Method Validation Report for Determination of Calcium Cation Concentration for Calcium Acetate Tablets In-Vitro Phosphate Binding Study')]. The report summary is summarized below:

Study Report Number	REP-07-196	REP-07-197
Analyte	Calcium Cation	Phosphate Anion
Internal standard (IS)	N/A	N/A
Method description	Ion Chromatography with Cation Suppressor and Conductivity Detector	Ion Chromatography with Anion Suppressor and Conductivity Detector
Limit of quantitation	5 mcg/mL	5 mcg/mL
% recovery	(b) (4)	%
Standard curve concentrations (mcg/mL)	5,25,30,40,50,60, and 70	5,10,20,30,40, and 50
QC Sample Concentrations (mcg/mL)	5,25,40 and 70 mcg/mL	5, 30 and 50 mcg/mL
System Suitability/Linearity	(b) (4)	
Precision		
Accuracy (%)		
Stability (days) (ambient)	2 days (sample solution)	7 days (sample solution)
Dilution integrity	Samples diluted $\leq$ 50 mcg/mL	Samples diluted $\leq$ 50 mcg/mL
Selectivity	Yes	Yes

	Test	**Reference**
Batch No.	CP06005	P4G114
Batch Size	(b) (4) Tablets	N/A
Manufacture Date	05/31/2006	N/A
Expiration Date	N/A	07/30/07
Potency	(b) (4) %	(b) (4) %
Content Uniformity (%)	(b) (4)	N/A

REVIEWER'S COMMENT:
The analytical method validation is incomplete. The firm did not provide within-study data (including all concentrations of standards and QCs; precision, accuracy and range) for Phosphate and Calcium analyses. The firm also did not provide mean, CV%, and % accuracy data for all standard and QC concentrations as part of the pre-study assay validation for calcium and phosphate.

3.6 In Vitro Studies

3.6.1 Phosphate Binding Assay

Study Summary, In Vitro Phosphate Binding Study

Study No.	REP-07-195
Study Design	In vitro Phosphate-Binding Study Report of Generic Calcium Acetate Tablets vs. Reference Listed Drug'
No. of units tested	2 units of test and reference, following complete dissolution and 24 hours of incubation with phosphate ions.
Test product	Calcium Acetate Tablets USP, 667 mg
Reference product	PhosLo® Tablets
Strength tested	667 mg

1.1. Calcium Acetate Tablet (Generic) Phosphate Binding Study

1.1.2. Sodium Phosphate Working Solutions Preparation

Sodium Phosphate working solutions were prepared as specified in the following table:

Level	0	1	2	3	4	5	6	7
Sodium Phosphate Tribasic (g)	0	1.07240	5.35730	10.71930	21.41870	37.46322	53.52902	107.0357
Final Volume (mL)	100	100	100	100	500	500	500	500
Concentration (mmole/mL)	0	0.02822	0.14098	0.28209	0.11273	0.19718	0.28173	0.56335

1.1.2. Phosphate Binding Time Determination

Three levels of the Phosphate Binding study were performed to determine the amount of time needed for incubation. Samples were taken at 30, 60, and 120 minutes for each level and analyzed for calcium concentration. The study results are shown in the following table:

Time Point (minutes)	Replicates	Calcium Peak Area of Phosphate Binding Samples		
		Level 1	Level 4	Level 7
30	1	11.00561	5.4450	0.0842
	2	10.5392	6.1762	0.0940
60	1	9.9909	6.1770	0.0891
	2	11.1081	6.4769	0.0644
120	1	10.7497	6.2361	0.0831
	2	11.6738	6.2383	0.0799

There was no significant difference of calcium peak area in each level of all the time points tested, which suggested that reaction between calcium and phosphate completed within 30 minutes. Since levels 1, 4 and 7 cover the entire concentration range for the phosphate binding study, the firm selected 30 minutes for the phosphate binding study for all 8 levels.

Reviewer's Note: In the pre-study method validation report, the firm provided phosphate concentration data for incubation beyond 30 minutes (120 minutes). The binding time study data showed that no additional binding occurred beyond 30 minutes of incubation.

1.1.3. Phosphate Binding for Test and RLD Products

Phosphate binding studies with 8 different phosphate concentration levels were conducted. For individual level, 12 vessels (labeled 1 to 12) were utilized. Equal amount of deionized water was added in all 12 vessels for each level (250 mL for levels 0 – 3; 240 mL for levels 4 – 7). One (1) tablet of test Calcium acetate Tablet was added to each of the vessels. After dissolution of the test calcium tablet, the freshly prepared sodium phosphate working solution for individual level was added into the corresponding vessels as specified below and incubated at 50 rpm paddle speed for 30 minutes:

Level	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Number of Vessels	12	12	12	12	12	12	12	12
Sodium Phosphate Working Solution (mL)	0	1.0	1.0	1.0	10.0	10.0	10.0	10.0
Amount of Sodium Phosphate Added (mmole)	***0***	***0.0282***	***0.1410***	***0.2821***	***1.1273***	***1.9718***	***2.8173***	***5.6335***
Amount of Water Added in each Vessel (mL)	250	250	250	250	240	240	240	240
Final Volume in Each Vessel	250	251	251	251	250	250	250	250

About 10 mL of solution was sampled after phosphate binding was completed. Samples were filtered and the filtrate analyzed for calcium and phosphate concentrations.

Calcium Amount in The Supernatant of Test Product Phosphate Binding Samples (in mg):

Sample	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6*	Level 7*
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	179.73	172.15	171.77	160.16	103.5	46.16	0.59	0.08
Reference	0659-15	0659-16	0659-21	0659-22	0659-23	0659-29	0659-29	0659-30

*Calcium concentration of level 6 and 7 phosphate binding samples were lower than the LLOQ (5 µg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate Amount in The Supernatant of Test Product Phosphate Binding Samples (in mg):

Sample	Level 0**	Level 1**	Level 2**	Level 3**	Level 4**	Level 5**	Level 6	Level 7
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	0.09	0.44	0.57	0.48	0.06	0.38	12.37	283.86
Reference	0659-39	0659-40	0659-40	0659-46	0659-47	0659-54	0659-55	0659-55

** Phosphate concentration of level 0 to5 phosphate binding samples were lower than the LLOQ (5 µg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate was quantitated only in two of the level 0 phosphate binding samples.

Calcium Amount in the Supernatant of RLD Phosphate Binding Samples (in mg):

Sample	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6*	Level 7*
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	**175.23**	**170.97**	**172.73**	**157.73**	**104.27**	**47.56**	***0.74***	***0.11***

*****Calcium concentration of level 6 and 7 phosphate binding samples were < LLOQ (5 mcg/mL), so the measured results were used for information only and were not used for statistical analysis.

Phosphate Amount in the Supernatant of RLD Phosphate Binding Samples (in mg):

Sample	Level 0*	Level 1*	Level 2*	Level 3*	Level 4*	Level 5*	Level 6	Level 7
1	(b) (4)							
2								
3								

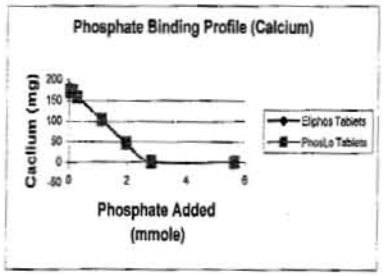
4	(b) (4)							
5								
6								
7								
8								
9								
10								
11								
12								
Average	***0***	***0.91***	***0.75***	***0.41***	***0.12***	***0.28***	**9.34**	**286.77**

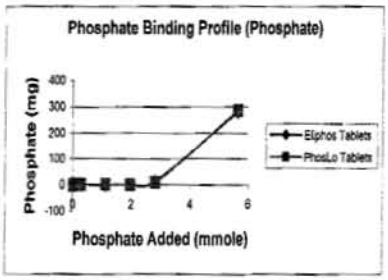
*****Phosphate concentration of level 0 to 5 phosphate binding samples were < LLOQ (5 mcg/mL), so the measured results were used for information only and were not used for statistical analysis. Phosphate anion was not detected in all the level 0 phosphate binding samples.

1.1.4. DATA ANALYSIS AND REPORT

1.1.4.1.Phosphate Binding Profile

The firm generated phosphate binding profiles by plotting free Phosphate vs. Amount of Sodium Phosphate and free Calcium vs. amount of Sodium Phosphate in each vessel. The **mean** profiles for both test and reference drug products for free calcium and free phosphate are shown in the following graphs (individual profiles are in the Attachment).





1.1.4.2.Determination of Phosphate Binding Capacity

The firm calculated the difference of the free phosphate concentration in level 0 and level 7. The difference in the values obtained and the original amount of Sodium Phosphate added into level 7 is considered as the phosphate bound by calcium acetate (maximum phosphate binding capacity). Phosphate anion was not detected in most level 0 phosphate binding samples except in two test drug samples where the concentrations are far below the LLOQ. With LLOQ of 5 mcg/mL and the average concentration of Phosphate in level 7, the uncertainty of phosphate concentration in level 0 samples has < 0.5% effect on the final phosphate binding capacity determination if Phosphate concentration of level 0 samples were assumed to 0 mcg/mL. Therefore, the firm based the calculation of phosphate binding capacity on 0 mg phosphate in level 0 phosphate binding samples for both the test and RLD.

Phosphate Binding Capacity for **Test** Drug (Level 7)

Sample	Phosphate (mg) Level 7	Phosphate (mmole) Level 7	Phosphate (mmole) Added Level 7	Phosphate Binding Capacity (mmole)	Log 10 Phosphate Binding	Natural Log Phosphate Binding
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	283.86	2.9880	N/A	2.6455	0.4223	**0.9724**
SD				0.0811	0.0135	0.0311

Phosphate Binding Capacity for **Reference** Drug (Level 7)

Sample	Phosphate (mg) Level 7	Phosphate (mmole) Level 7	Phosphate (mmole) Added Level 7	Phosphate Binding Capacity (mmole)	Log 10 Phosphate Binding	Natural Log Phosphate Binding
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	286.77	3.0186	N/A	2.6149	0.4171	**0.9605**
SD				0.1054	0.0176	0.0405

Phosphate Binding Capacity for **Test** Drug (Level 6) – Compiled by Reviewer

Sample	Phosphate (mg) in Level 6	Phosphate (mg) Added Level 6	Phosphate Binding Capacity (mg)	Natural Log Phosphate Binding
1				(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				

11		(b) (4)		
12				
Mean	12.62	N/A	254.94	**5.54**
SD	**1.68**		1.68	0.0066

Phosphate Binding Capacity for **Reference** Drug (Level 6) – Compiled by Reviewer

Sample	Phosphate (mg) in Level 6	Phosphate (mg) Added Level 6	Phosphate Binding Capacity (mg)	Natural Log Phosphate Binding
1		(b) (4)		
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	9.34	N/A	258.22	**5.55**
SD	1.85		1.85	0.0072

1.1.4.3. Statistical Analysis By Firm (Using only Level 7)

The firm calculated the 90% confidence intervals of the maximum binding capacity of the generic and RLD products.

Ln-transformed Phosphate Binding Data – Firm Calculated

	Mean	90% CI	
Test	0.9724	95.63	98.85
Reference	0.9604	93.95	98.14
T/R	**1.0124**		

Reviewer's Note:
The firm did not calculate the 90% confidence interval for the difference between formulations. The test and RLD formulations were not compared using ANOVA model with formulation as the classification variable.

b) In Vitro Results

3.6.1.1

Table 1 Calcium Amount (mg) in the Supernatant after Binding – Calculated by Reviewer.

Phosphate Spiking Level (mmoles)	LSMean (mg)		LSMean Ratio	
	Test	Reference	Point Estimate	90%CI
0 (0.0)*	179.73	175.23	1.03	100.0 – 105.3
1 (0.0282)	172.15	170.97	1.01	98.3 – 103.3
2 (0.1410)	171.77	172.70	0.99	97.3 – 101.8
3 (0.2821)	160.16	157.73	1.02	97.1 – 106.6
4 (1.1273)	103.5	104.27	0.99	96.5 – 98.7
5 (1.9718)	46.16	47.56	0.97	94.9 – 99.3
6 (2.8173)	0.00	0.00	N/A	N/A
7 (5.6335)	0.00	0.00	N/A	N/A

*****Binding capacity fully demonstrated at Level 0.

Similarity Factor F2: 80.3 (calculated using mean calcium concentrations of all 6 levels)

Comments: Binding capacity of Calcium tablet = Amt of Calcium (mg) in level 0 minus Amt of Calcium (mg) in Level 7. The following acceptance conditions were satisfactory met from Level 0 to 5: 1) evaluation of binding capacity within acceptable 90% CI limits (80 – 125%); 2) point estimate within the established acceptance limit of (90 – 110%); 3) F2 > 80. Levels 6 and 7 below LLOQ and are given the value of zero.

Table 2 Phosphate Amount (mg) in the Supernatant after Binding – calculated by Reviewer.

Phosphate Spiking Level (mmoles)	LSMean (mg)		LSMean Ratio	
	Test	Reference	Point Estimate	90%CI
0 (0.0)*	0.00	0.00	N/A	N/A
1 (0.0282)	0.00	0.00	N/A	N/A
2 (0.1410)	0.00	0.00	N/A	N/A
3 (0.2821)	0.00	0.00	N/A	N/A
4 (1.1273)	0.00	0.00	N/A	N/A
5 (1.9718)	0.00	0.00	N/A	N/A
6 (2.8173)	12.37	9.34	1.37	N/A
7 (5.6335)	283.86	286.77	0.99	N/A

Similarity Factor F2: 75.19 (calculated using mean phosphate concentrations of all 2 levels)

Comments: The Phosphate concentrations in the supernatant are all zero except at the last two levels (Levels 6 and 7). The point estimate at Level 6 is outside the acceptance limit (90-110%). However, this is acceptable since the data are for supportive purpose only.

3.7 Formulation

Location in appendix	Section 3.13, Page 19
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	Acceptable
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.3, page 14
Source of Method (USP, FDA or Firm)	USP
Medium	Purified water
Volume (mL)	900mL
USP Apparatus type	Type II (paddle)
Rotation (rpm)	50rpm
DBE-recommended specifications	Not less than (b) (4) (Q) in 30 minutes.
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Acceptable
If not then why?	N/A

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
N/A			

3.9 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	N/A

3.10 Deficiency Comments

1. The firm did not submit raw numerical data of all standards, QCs and samples used in the binding study. The raw data should include peak area/height data and calculated concentration data before corrected for dilution, and also final concentration data after corrected for dilution.

2. The firm did not summarize the standard and QC data of both calcium and phosphate from the Binding Study (REP-07-195). The summary tables should be in a similar format as in the table shown below:

	Calcium (µg/mL) Number of QCs included				**Phosphate (µg/mL) Number of QCs included**			
QC Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Cal. Standards Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Linearity Range (range of R^2 values)								

3. The firm did not submit at least 20% of the chromatograms of Calcium and Phosphate analysis.

4. The firm did not submit a list of all repeat study samples with original values and final reported values, and the reasons for reanalysis and reporting final values.

5. The firm did not submit relevant bioanalytical SOPs

6. The firm is requested to provide the dates of the binding study and sample analysis.

3.11 Recommendations

The repeat in vitro phosphate binding BE study conducted by Cypress Pharmaceutical on its Calcium Acetate Tablets USP, 667 mg, comparing it with the reference product, Nabi's PhosLo® Tablets, 667 mg, is incomplete due to the deficiency comments above.

The firm should be informed of the deficiency comments.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	

3.13 Formulation Data

Table 2.3.P.1-3. Unit Composition of ELIPHOS Tablets				
Compound	**Reference to Quality Standard**	**Function**	**Quantity per Unit**	
			(mg/tablet)	**(% w/w)**
Calcium Acetate	*USP*	Drug substance	(b) (4)	
Polyethylene Glycol 8000	*NF*		(b) (4)	
Sodium Lauryl Sulfate	*NF*			
Crospovidone	*NF*			
Total Tablet Weight			(b) (4)	100.0
[a] = Equivalent to 667 mg on anhydrous basis (assuming water content of (b) (4) % w/w)				

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Inactive ingredients are within IIG limits

3.14 Dissolution Data

Dissolution Review Path	None

Table 4. Dissolution Data

Dissolution Conditions	**Apparatus:**	Paddle
	Speed of Rotation:	50 rpm
	Medium:	Multiple Media (0.1 N HCl, pH 4.5 Acetate Buffer, Deionized Water)
	Volume:	900 mL
	Temperature:	37^0C
Firm's Proposed Specifications	NLT (b) (4) (Q) in 30 minutes.	

A study was conducted to compare the dissolution profile of the proposed drug product to that of the RLD. For this purpose, dissolution tests according to the *USP* specification were performed in three different pH media for both the RLD and the proposed drug product. Results of this study are summarized below:

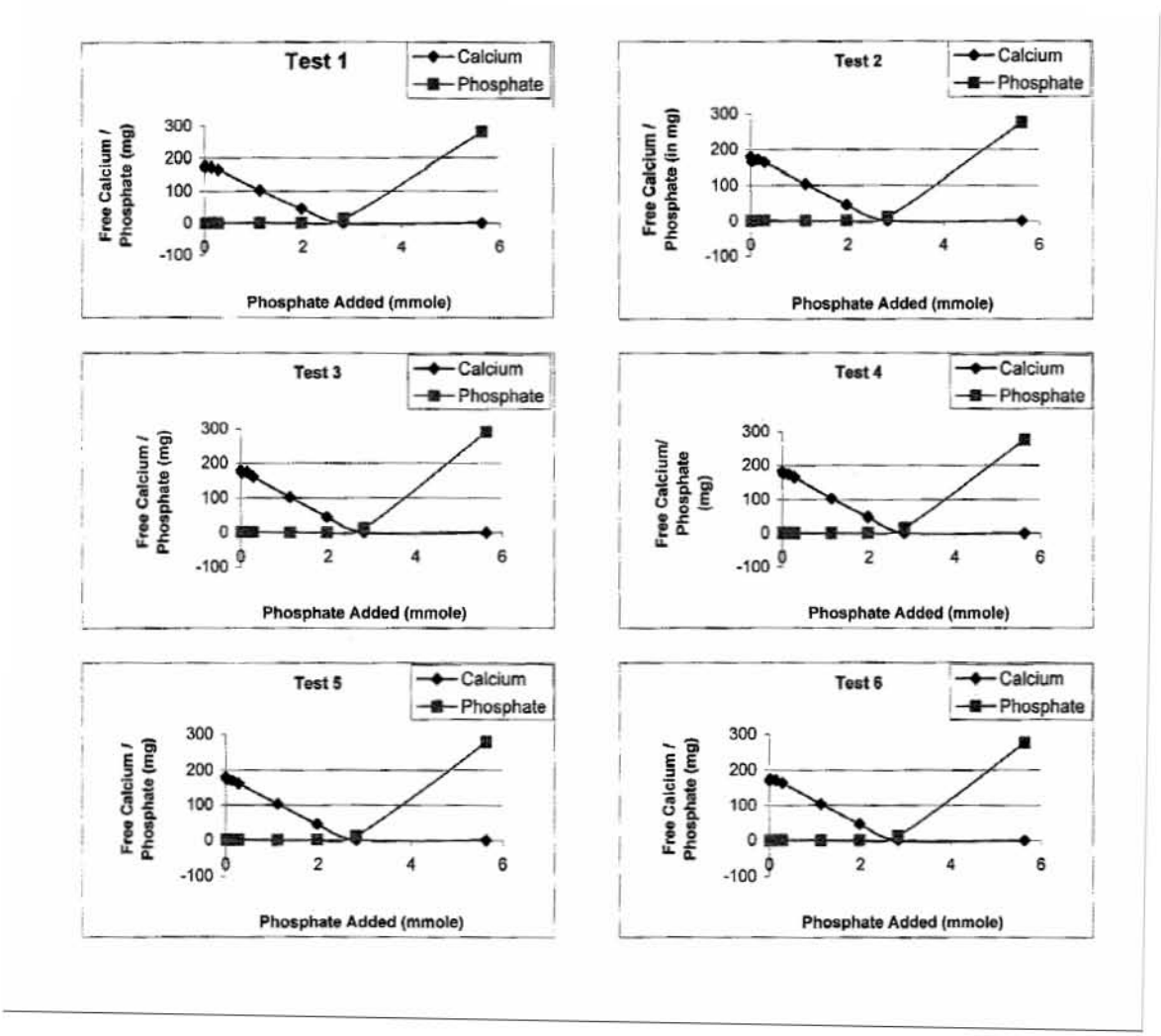
Medium	**DI Water**	
	Calcium Acetate Tablets	**PhosLo®**
Tablets	**% Release at 15 minutes**	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	100
Range	100-101%	95-104%

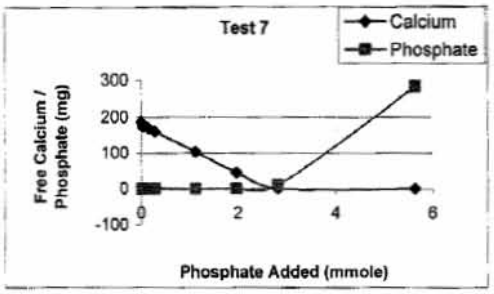
Medium	0.1 N HCl	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	101
Range	100-101%	98 – 104%

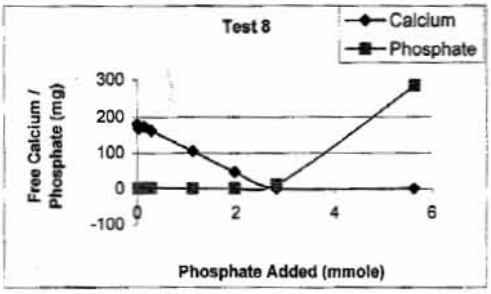
Medium	pH 4.5 Acetate Buffer	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	100	102
Range	93-104%	99-105%

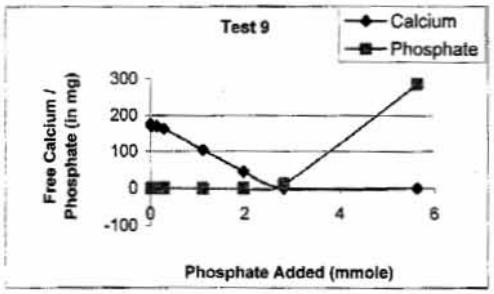
15 Pages of SAS datasets have been Withheld as b4 (TS/CCI) immediately following this page

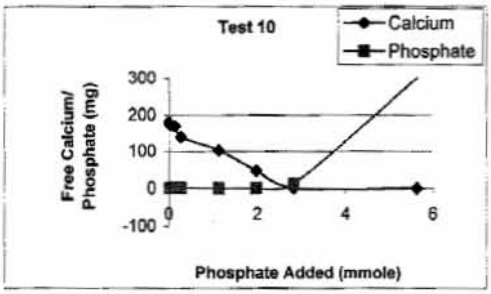
Attachment I

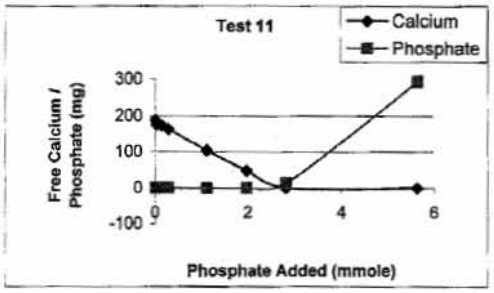


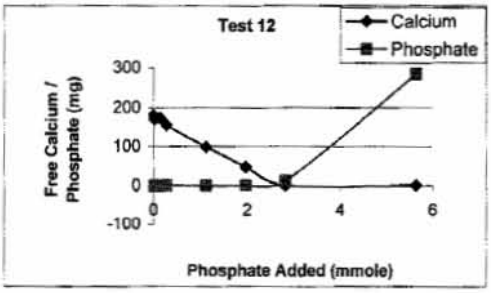

Test 7
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

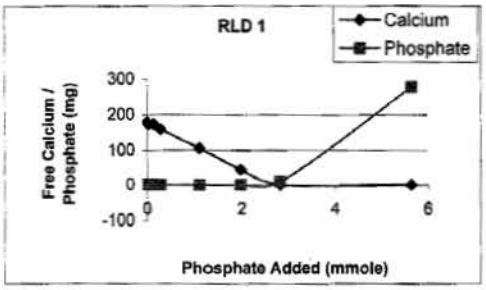

Test 8
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

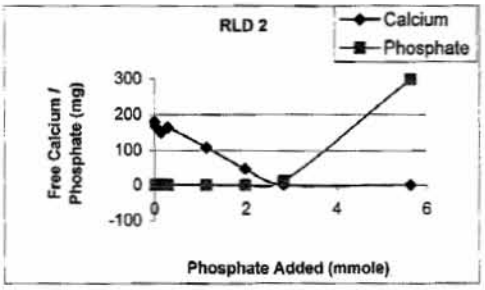

Test 9
Calcium
Phosphate
Free Calcium / Phosphate (in mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

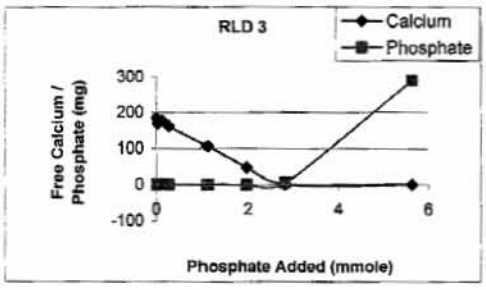

Test 10
Calcium
Phosphate
Free Calcium/ Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

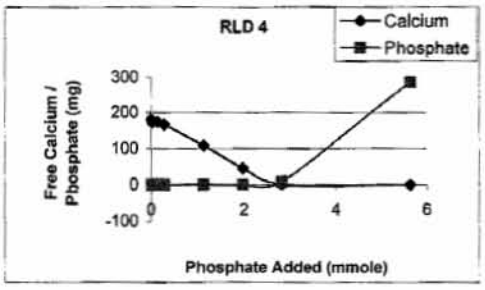

Test 11
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

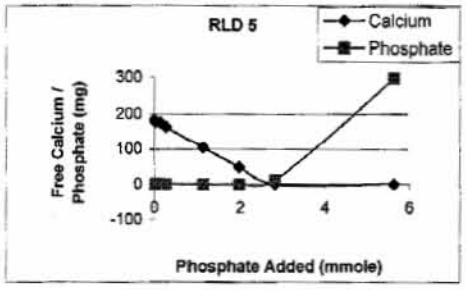

Test 12
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

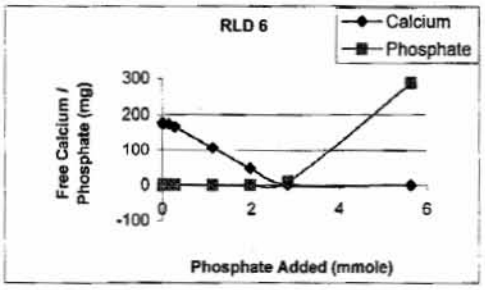

RLD 1
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

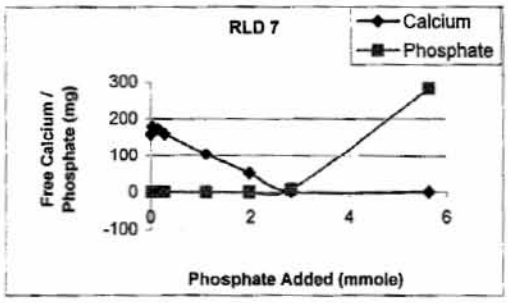

RLD 2
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

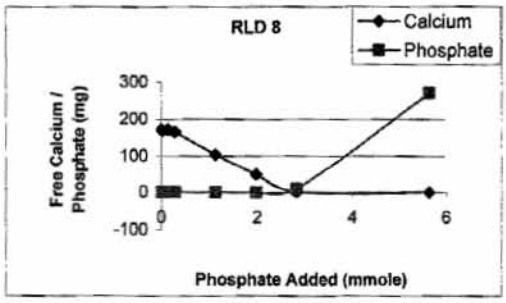

RLD 3
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

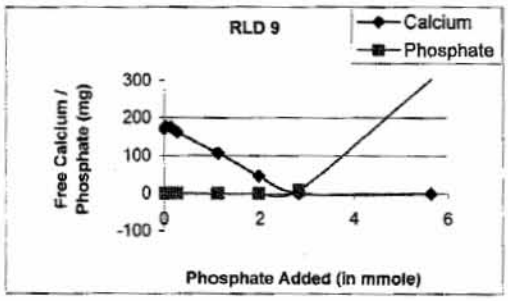

RLD 4
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

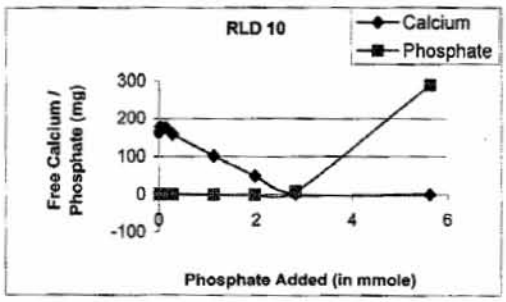

RLD 5
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

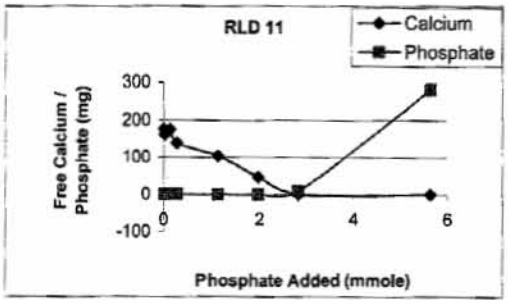

RLD 6
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

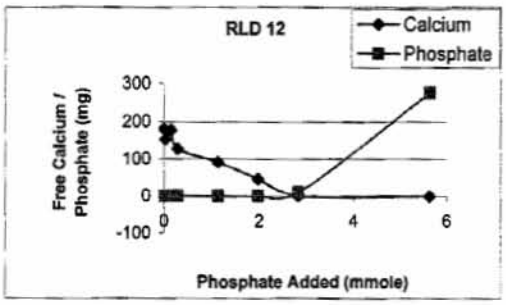

RLD 7
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)


RLD 8
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)


RLD 9
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (in mmole)


RLD 10
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (in mmole)


RLD 11
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)


RLD 12
Calcium
Phosphate
Free Calcium / Phosphate (mg)
300
200
100
0
-100
0
2
4
6
Phosphate Added (mmole)

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 78-502

APPLICANT: Cypress Pharmaceutical,Inc.

DRUG PRODUCT: Calcium Acetate Tablets USP, 667mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified in the report of the in vitro binding BE study No. REP-07-195.

1. Please submit raw numerical data of all standards, QCs and samples used in the binding study. The raw data should include peak area/height data and calculated concentration data before corrected for dilution, and also final concentration data after corrected for dilution.

2. Please summarize the standard and QC data of both calcium and phosphate from the Binding Study (REP-07-195). The summary tables should be in a similar format as in the table shown below:

	Calcium (µg/mL) **Number of QCs included**				**Phosphate (µg/mL)** **Number of QCs included**			
QC Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Cal. Standards Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Linearity Range (range of R^2 values)								

3. Please submit at least 20% of the chromatograms of Calcium and Phosphate analysis.

4. Please submit a list of all repeat study samples with original values and final reported values, and the reasons for reanalysis and reporting final values.

5. Please submit relevant bioanalytical SOPs.

6. Please provide the dates of the binding study and sample analysis.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Outcome Page

ANDA: 78-502

Completed Assignment for 78502 ID: 5321

Reviewer: Nwakama, Patrick **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5321	12/27/2007	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Patrick E. Nwakama
5/7/2008 09:14:47 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
5/7/2008 01:00:45 PM
BIOPHARMACEUTICS

Moheb H. Makary
5/7/2008 01:05:40 PM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-502	
Drug Product Name	Calcium Acetate Tablets USP, 667mg	
Strength(s)	EQ 169mg Calcium	
Applicant Name	Cypress Pharmaceutical Inc.	
Address	135 Industrial Blvd, Madison, MS 39110	
Applicant's Point of Contact	Robert L. Lewis	
Contact's Telephone Number	(800) 856-4393	
Contact's Fax Number	(601) 853-1567	
Original Submission Date(s)	October 16, 2006	
Submission Date(s) of Amendment(s) Under Review	N/A	
Reviewer	Patrick Nwakama, Pharm.D.	
Study Number (s)	REP-06-022	REP-06-027
Study Type (s)	In vitro Phosphate Binding Study	In vitro multi-pH Dissolution Study
Strength (s)	667 mg	667 mg
Clinical Site	N/A	
Clinical Site Address	N/A	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	

1 EXECUTIVE SUMMARY

The firm has submitted the results for in-vitro dissolution testing and *in-vitro* phosphate binding study to establish bioequivalence (BE) of the firm's Calcium Acetate Tablet USP, 667mg, with the RLD products, PhosLo® Tablet, 667mg from NABI Biopharmaceuticals.

The dissolution testing is acceptable. The DBE acknowledges that the firm conducts the dissolution testing using the USP method and specification. The dissolution testing of the test and RLD products in various pH media is also acceptable.

The firm did not conduct the *in vitro* phosphate binding study as recommended by the DBE. The firm determined relative *in vitro* phosphate binding (test vs. RLD) by measuring the amount of calcium phosphate precipitate using gravimetric analysis and not by analyzing the free calcium and free phosphate in the supernatant after precipitation using a validated analytical method as recommended by the DBE. In addition, the firm did not use several concentrations (0 to 5.6334 mMoles) of the phosphate solution at one incubation time point as recommended by the DBE. It is further noted that higher concentrations of sodium phosphate may be necessary to achieve complete phosphate precipitation capacity, and a meaningful phosphate binding profile. The application is **incomplete.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Calcium Acetate Tablets USP, 667mg
Reference Product	PhosLo® Tablets
RLD Manufacturer	Nabi Biopharmaceuticals
NDA No.	19-976
RLD Approval Date	December 10, 1990
Indication	Management of hyperphosphatemia in end stage renal failure

3.2 PK/PD Information

Bioavailability	Not applicable. The product acts by binding locally in the GI tract with phosphate present in ingested food.
Food Effect	This product's mode of action is through removing phosphate from food the subject ingests, and is, therefore, subject to oral food effects.
Tmax	Not Available. Calcium levels not determinable in blood.
Metabolism	Not applicable
Excretion	Calcium acetate is excreted in the form of calcium phosphate in the feces and as calcium in the urine.
Half-life	Not applicable.
Drug Specific Issues (if any)	It combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Calcium acetate is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine. Therefore, this is a locally acting, not systemically acting, drug product.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, in vitro phosphate binding and multiple pH dissolution profiles

1.	**Type of study:**	in vitro phosphate binding
	Design:	In vitro reaction of calcium in the drug product to a prepared phosphate solution, followed by gravimetric analysis of **bound** phosphate.
	Strength:	667 mg
	Subjects:	N/A
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	Phosphate binding of the test product $\geq$ 90% that of the RLD
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	OGD #06-1117; [redacted] (b) (4); 10/25/06

Summary of OGD or DBE History (for details, see Appendix 4.4):	The DBE recommends the following alternative phosphate binding protocol designed to provide (i) phosphate binding capacity of the test and reference drug product, and (ii) phosphate binding profiles of the test and reference drug products that are useful for determination of bioequivalence of the drug product. The procedure below, describing one set of data, should be performed 12 times each for test and reference products. The study consists of the following: • Completely dissolve a tablet or capsule in an appropriate volume in vessels for test and reference separately. • In deionized water, prepare solutions with amounts of Na_3PO_4 ranging from 0.0 mMoles to 5.6334 mMoles. • Add the appropriate Na_3PO_4 solution to the dissolved Calcium Acetate tables or capsules and incubate until complete precipitation has occurred. • Separate the supernatant from the precipitate using an appropriate method. • Measure the free calcium and free phosphate in the supernatant using a validated analytical method. Present the data for mMoles (or mg) of calcium and phosphate in the supernatant of the vessels. Determine the phosphate binding capacity in mMoles (or mg) using an appropriate method. Vessel data may be used to provide the phosphate binding profile. Compare the T/R binding capacity ratios. In addition, the DBE recommended the following dissolution testing: USP Apparatus II (Paddle) at 50 RPM and USP Apparatus I (Basket) @ 100 RPM Medium: water, 0.1 N HCl, acetate buffer pH 4.5, borate buffer pH 6.8 Volume: 900 ml Sampling time: 5, 10, 15 and 30 minutes. **Literature Review:** In the Journal of Pharmaceutical and Biomedical Analysis Vol.19 pages 911-915, 1999, the authors describe an in-vitro phosphate binding assay for sevelamer. The product was incubated with mixing for 15min in phosphate solution concentrations ranging from 10-18mM that was buffered to pH7.0 with BES.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	1

Waiver requests	No	0
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.5 Pre-Study Bioanalytical Method Validation

Not provided

Comments on the Pre-Study Method Validation: The firm did not provide pre-study validation.

3.6 In Vitro Studies

3.6.1 Phosphate Binding Assay

Study Summary, In Vitro Phosphate Binding Study	
Study No.	REP-06-022
Study Design	In Vitro measurement of phosphate binding capacity and phosphate binding profiles of the test and RLD products in solutions of a single phosphate concentration.
No. of units tested	2 units of test and reference, following complete dissolution and 24 hours of incubation with phosphate ions.
Test product	Calcium Acetate Tablets USP, 667mg
Reference product	PhosLo® Tablets
Strength tested	667 mg

Percent Relative Phosphate Binding (Test/Reference) Calculated By the firm:

% Phosphate Binding (Test Tablets) = Weight of Precipitate from Calcium Acetate Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424 g.

= (b) (4)

% Phosphate Binding (PhosLo® Tablets) = Weight of Precipitate from PhosLo® Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424

= (b) (4)

% Phosphate Binding (Test/Reference) = % Phosphate Binding (Calcium Acetate Tablets) x 100%
% Phosphate Binding (PhosLo® Tablets)

= (b) (4)

= 96.38%

Comments on in vitro Study: The firm did not provide assay method validation data and the phosphate binding study is not conducted as currently recommended by the DBE.

3.7 Formulation

Location in appendix	Section 4.2, Page 13
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	Acceptable
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.3, page 14
Source of Method (USP, FDA or Firm)	USP
Medium	Purified water
Volume (mL)	900mL
USP Apparatus type	Type II (paddle)
Rotation (rpm)	50rpm
DBE-recommended specifications	Not less than (b) (4) (Q) in 30 minutes.
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Acceptable
If not then why?	N/A

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
N/A			

3.9 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	N/A

3.10 Deficiency Comments

1. The firm determined comparative phosphate binding capacity of the test product vs. the reference by measuring the amount of calcium phosphate precipitate using gravimetric analysis. As currently recommended by DBE, the firm did not analyze free calcium and free phosphate in the supernatant once precipitation has occurred using a validated analytical method. The firm also did not use varying concentrations (0 to 5.6334 mMoles) of the phosphate solution at one incubation time point as recommended by the DBE for demonstration of in vitro bioequivalence.

2. The firm did not provide both pre-study and within study validation data.

3. The firm did not provide bio-batch size and content uniformity for the test product.

3.11 Recommendations

1. The in vitro phosphate binding BE study conducted by Cypress Pharmaceutical on its Calcium Acetate Tablets USP, 667 mg, comparing it with the reference product, Nabi's PhosLo® Tablets, 667 mg, is incomplete due to the reasons cited in the deficiency comments above.

2. The dissolution testing conducted by Cypress Pharmaceutical on its Calcium Acetate Tablets USP, 667 mg, is acceptable.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 In vitro Bioequivalence Study

4.1.1.1 Study Design

Table 1 Study Information

Study Number	REP-06-022
Study Title	In Vitro measurement of phosphate binding capacity and phosphate binding profiles of the test and RLD products in solutions of a single phosphate concentration.
Study Sponsor	Cypress Pharmaceutical
Analytical Site (Name & Address)	(b) (4)
Analytical Director	Not provided
Analysis Dates	Not provided
No. of Units Tested	2 units of test and reference, following complete dissolution and 24 hours of incubation with phosphate ions.
Acceptance Criteria	*in vitro* phosphate binding capacity of the test product is ≥ 90% of that of the RLD.

Table 2. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Calcium Acetate Tablets USP, 667mg	PhosLo® Tablets
Manufacturer	(b) (4)	Nabi Biopharmaceuticals
Batch/Lot No.	CP06005	NC060009
Manufacture Date	Not provided	
Expiration Date		10/07
Strength	667 mg	667 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	Not provided	
Production Batch Size	Not provided	
Potency (Assay)	(b) (4)%	Not provided
Content Uniformity (mean, %CV)	Not provided	

Phosphate Binding Study Procedure:

The test was performed in duplicate.

1. (b) (4)
2.
3.
4.
5.
6.

Comments on Study Design: Not acceptable. The firm should conduct the in vitro binding study using the DBE-recommended procedure.

4.1.1.2 In Vitro Results

For phosphate binding capacity, the firm reported the amount (in grams) of calcium phosphate precipitate as shown in the Table below:

Sample	Filter Paper (g)	Filter Paper + Precipitate (Dried)(g)	Precipitate (Dried)(g)	Average (g)
Calcium Acetate Standard-1	(b) (4)			
Calcium Acetate Standard-2				
PhosLo®-1				
PhosLo®-1				
Calcium Acetate Tablets-1				
Calcium Acetate Tablets-2				

*The firm reported that its previous in-house study showed that there is (b) (4)% water content in calcium acetate, USP, the weight of precipitate from calcium acetate standard = 0.27424 g.

% Phosphate Binding (Calcium Acetate Tablets) (Lot # CP06005)
= Weight of Precipitate from Calcium Acetate Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424 g.

= (b) (4)

% Phosphate Binding (PhosLo® Tablets)
= Weight of Precipitate from PhosLo® Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424

= (b) (4)

% Phosphate Binding (Test/Reference)
= % Phosphate Binding (Calcium Acetate Tablets) x 100%
% Phosphate Binding (PhosLo® Tablets)

= (b) (4)

= 96.38%

4.1.1.3 Assay Validation Results

The firm did not provide standard and QC data for both pre-study and during-study validation.

4.1.1.4 In vitro Study Results

For phosphate binding capacity, the firm reported the amount (in grams) of calcium phosphate precipitate as shown in the Table below:

Sample	Filter Paper (g)	Filter Paper + Precipitate (Dried)(g)	Precipitate (Dried)(g)	Average (g)
Calcium Acetate Standard-1				
Calcium Acetate Standard-2				
PhosLo®-1				
PhosLo®-1				
Calcium Acetate Tablets-1				
Calcium Acetate Tablets-2				

(b) (4)

*The firm reported that its previous in-house study showed that there is (b) (4)% water content in calcium acetate, USP, the weight of precipitate from calcium acetate standard = 0.27424 g.

% Phosphate Binding (Calcium Acetate Tablets) (Lot # CP06005)
= Weight of Precipitate from Calcium Acetate Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424 g.

= (b) (4)

% Phosphate Binding (PhosLo® Tablets)
= Weight of Precipitate from PhosLo® Tablet (g) x 100%
Weight of Precipitate from Standard (g)

= (b) (4) g x 100%
0.27424

= (b) (4)

% Phosphate Binding (Test/Reference)
= % Phosphate Binding (Calcium Acetate Tablets) x 100%
% Phosphate Binding (PhosLo® Tablets)

= (b) (4)

= 96.38%

4.1.1.5 Assay Validation Results

The firm did not provide standard and QC data for both pre-study and during-study validation.

4.2 Formulation Data

Table 2.3.P.1-3. Unit Composition of ELIPHOS Tablets

Compound	Reference to Quality Standard	Function	Quantity per Unit (mg/tablet)	Quantity per Unit (% w/w)
Calcium Acetate	*USP*	Drug substance	(b) (4)	
Polyethylene Glycol 8000	*NF*		(b) (4)	
Sodium Lauryl Sulfate	*NF*			
Crospovidone	*NF*			
Total Tablet Weight			(b) (4)	100.0

[a] = Equivalent to 667 mg on anhydrous basis (assuming water content of (b) (4)% w/w)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Inactive ingredients are within IIG limits

4.3 Dissolution Data

Dissolution Review Path	None

Table 4. Dissolution Data

Dissolution Conditions	**Apparatus:**	Paddle
	Speed of Rotation:	50 rpm
	Medium:	Multiple Media (0.1 N HCl, pH 4.5 Acetate Buffer, Deionized Water)
	Volume:	900 mL
	Temperature:	37^0C
Firm's Proposed Specifications	NLT (b) (4) (Q) in 30 minutes.	

A study was conducted to compare the dissolution profile of the proposed drug product to that of the RLD. For this purpose, dissolution tests according to the *USP* specification were performed in three different pH media for both the RLD and the proposed drug product. Results of this study are summarized below:

Medium	**DI Water**	
	Calcium Acetate Tablets	**PhosLo®**
Tablets	**% Release at 15 minutes**	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	100
Range	100-101%	95-104%

Medium	0.1 N HCl	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	101	101
Range	100-101%	98 – 104%

Medium	pH 4.5 Acetate Buffer	
	Calcium Acetate Tablets	PhosLo®
Tablets	% Release at 15 minutes	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average	100	102
Range	93-104%	99-105%

Figure 1. Dissolution Profiles

N/A

4.4 Detailed Regulatory History (If Applicable)

N/A

4.5 Consult Reviews

N/A

4.6 Additional Attachments

N/A

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 78-502

APPLICANT: Cypress Pharmaceutical,Inc.

DRUG PRODUCT: Calcium Acetate Tablets USP, 667mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified in the report of the in vitro binding BE study No. REP-06-022.

1. Your phosphate binding study procedure is not acceptable, because it is not designed for the determination of the phosphate precipitation capacity. You determined relative phosphate binding capacity (test/reference) by measuring the amount of calcium phosphate precipitate by gravimetric analysis and not by analyzing the free calcium and free phosphate in the supernatant once precipitation has occurred. In addition, your experiment was conducted using only one concentration of phosphate solution at one time point. To demonstrate bioequivalence using in vitro phosphate-binding capacity of the drug products (test vs. reference), you need to conduct an equilibrium experiment on the drug products that uses several concentrations (e.g., 0 to 5.6334 mMoles or higher) of phosphate solution at one incubation time point as described below.

2. Please repeat your in vitro phosphate binding study as **outlined** below:

   a. Prepare eight vessels for test and eight vessels for reference. Completely dissolve one calcium phosphate tablet or capsule in appropriate volume of deionized water.
   b. Add varying amounts of sodium phosphate (Na_3PO4) in the eight incubation vessels (e.g., 0.0, 0.02817, 0.14084, 0.28167, 1.12668, 1.97169, 2.8167 and 5.6334 mMoles). Please note higher than 5.6334 mMoles of sodium phosphate may be necessary to achieve complete phosphate precipitation capacity and a meaningful phosphate binding profile. Accordingly, more than 8 vessels for test and reference will be required.
   c. Incubate at 37°C in a shaking water bath until complete precipitation has occurred.

d. Separate the supernatant using appropriate method, e.g., centrifugation or vacuum filtration.
e. Measure the free calcium and free phosphate in the supernatant using validated analytical methods.
f. Carry out the binding assay (steps a-e) on 12 replicates each for test and reference products.
g. Present the data (mMole or mg) for calcium and phosphate (PO_4) in the supernatant in table format.
h. The phosphate binding capacity (maximum binding) is determined from the mMoles (or mg) difference between Vessel 1 and Vessel 8 or more as the case may be).
i. A plot of data from Vessels 1 through 8 (or more as the case may be) will provide the phosphate binding profile.
j. Compare the mean of maximum binding for test to the mean of maximum binding for reference (T/R binding ratios). For binding capacity, the T/R ratio should fall within ±10% (0.9 to 1.1). Please also provide a 90% confidence interval (transferred and log-transformed data) of the maximum binding capacity of the test and reference. The DBE will set an interim specification upon review of the submitted results. The similarity factor (f2) may be used to compare the mean profiles for the test and reference products.

3. Please develop sensitive, specific and validated analytical methods for measuring phosphate and calcium. Please provide pre-study and during study data (including all concentrations of standards and QCs; precision, accuracy and range) for Phosphate and Calcium analyses. Please provide bio-batch size and content uniformity for the test product. Please refer to the FDA guidance, Bioanalytical Method Validation (Issued 5/2001) for more information.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.7 Outcome Page

ANDA: 78-502

1.	**Other**	Strength:	667 mg
	(OTH)	Outcome:	**IC**
	Type:	In Vitro Binding Study	
	Submission Date(s)		

BIOEQUIVALENCE OUTCOME DECISIONS:	IC – Incomplete

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/s/

Patrick E. Nwakama
8/29/2007 07:55:00 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
8/29/2007 10:14:16 AM
BIOPHARMACEUTICS

Dale Conner
8/29/2007 11:30:26 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-502

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-502 Applicant Cypress Pharmaceuticals
Drug Calcium Acetate Strength(s) 667 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 20 Nov 2008 Initials MHS	Date 11/24/08 Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = PhosLo NDA# 19-976
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 10/17/2006, BOS=Phos-Lo NDA 19-976, PIII cert to '105 patent provided. At the time of submission the NDA Phos-Lo Tablets was in the D/C'd section of the OB. The sponsor submitted CP 2006-0399 requesting that the Agency formally determine whether NDA 19-976 was D/C'd for S/E reasons. ANDA ack for filing 10/17/2006 (LO dated 1/19/2007. The electronic OB now reflects that NDA 19-976 was not D/C'd for S/E reasons. All patents have now expired. This ANDA is eligible for Full Approval.

2. Project Manager, Ben Danso Team5 Review Support Branch	Date 11-19-08 Initials BD	Date _____ Initials _____

Original Rec'd date 10-16-06
Date Acceptable for Filing 10-17-06
Patent Certification (type) P III
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3-7-08
Date of Office Bio Review 7-2-08
Date of Labeling Approv. Sum 11-2-07
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☒

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date _____	Date 11/24/08
Name/Initials _____	Name/Initials rlw/for

Comments:
Final-printed labeling (FPL) found acceptable for approval 11/2/07.
Proprietary name (Eliphos) also found acceptable by DMETS.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 11/24/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date11/20/08
Chemistry Div. I II OR III Initialsps
Comments: CMC O.K.

6. Frank Holcombe **First Generics Only** Date 11/24/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Roxane's ANDA 77-693 for this drug product was approved on January 30, 2008.

7. Vacant Date
Deputy Dir., DLPS Initials
RLD = PhosLo Tablets 169 mg (base)
Fresenius Medical Care North America NDA 19-976

8. Peter Rickman Date 11/24/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies (in-vitro phosphate binding study and in-vitro multi-pH dissolution studies found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 7/2/08.

Final-printed labeling (FPL) found acceptable for approval 11/2/07.

CMC found acceptable for approval (Chemistry Review #2) 11/17/08.

OR

8. Robert L. West Date 11/24/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 3/7/08 (Verified 11/24/08). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

The RLD, PhosLo Tablets, is currently in the discontinued section of the "Orange Book". In a Federal Register notice issued on July 31, 2007, the agency announced its determnation that PhosLo Tablets were not withdrawn from the market for reasons of safety or effectiveness.

This ANDA is recommended for approval.

9. Gary Buehler Date 11/24/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Ben Danso Date
Review Support Branch Initials

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
_____Time notified of approval by phone
_____Time approval letter faxed

FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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/s/

Benjamin Danso

11/24/2008 03:21:57 PM

BIOEQUIVALENCY AMENDMENT

ANDA 78-502

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Cypress Pharmaceuticals, Inc. US
Agent: Beckloff Associates, Inc.

TEL:

FAX: 800-856-4393, 601-853-1567

ATTN: Robert L. Lewis

PROJECT MANAGER: (240) 276-8782

FROM: Aaron Sigler

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on October 16, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcium Acetate Tablets USP, 667 mg.

Reference is also made to your amendment dated December 27, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**2**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 78-502

APPLICANT: Cypress Pharmaceutical,Inc.

DRUG PRODUCT: Calcium Acetate Tablets USP, 667mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified in the report of the in vitro binding BE study No. REP-07-195.

1. Please submit raw numerical data of all standards, QCs and samples used in the binding study. The raw data should include peak area/height data and calculated concentration data before corrected for dilution, and also final concentration data after corrected for dilution.

2. Please summarize the standard and QC data of both calcium and phosphate from the Binding Study (REP-07-195). The summary tables should be in a similar format as in the table shown below:

	Calcium (µg/mL) Number of QCs included				**Phosphate (µg/mL) Number of QCs included**			
QC Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Cal. Standards Conc.								
Inter day Precision (%CV)								
Inter day Accuracy (%)								
Linearity Range (range of R^2 values)								

3. Please submit at least 20% of the chromatograms of Calcium and Phosphate analysis.

4. Please submit a list of all repeat study samples with original values and final reported values, and the reasons for reanalysis and reporting final values.

5. Please submit relevant bioanalytical SOPs.

6. Please provide the dates of the binding study and sample analysis.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Barbara Davit

5/7/2008 05:12:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-502

Beckloff Associates, Inc.
U.S. Agent for Cypress Pharmaceutical, Inc.
Attention: William C. (Trey) Putnam, Ph.D.
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated January 3, 2007 and your correspondence dated January 11, 2007.

NAME OF DRUG: Calcium Acetate Tablets USP, 667 mg

DATE OF APPLICATION: October 16, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 17, 2006

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Benjamin Danso
Project Manager
301-827-5763

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer
1/19/2007 02:29:48 PM
Signing for Wm Peter Rickman

MINOR AMENDMENT

ANDA 78-502

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Cypress Pharmaceutical, Inc. TEL: 913-451-3955
US Agent: Berkloff Associates, Inc.
ATTN: William C. Putnam FAX: 913-451-3846

FROM: Benjamin Danso PROJECT MANAGER: (301) 827-5763

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcium Acetate Tablets USP, 667 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**2**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

III. List of Deficiencies to Be Communicated.

ANDA: 78-502 APPLICANT: Cypress Pharmaceutical, Inc.

DRUG PRODUCT: Calcium Acetate Tablets USP, 667 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

[redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. For future submissions, please be advised that you need to include the following in the QOS: The drug substance and drug

product specifications, description of manufacturing process, flow diagram, and a tabular summary of the analytical method, validation report, critical in-process tests etc.
Please refer to the model QOS in the OGD web site for organization of QOS:

http://www.fda.gov/cder/ogd/QbR/QbR%20Frequently%20Asked%20Questions%20June2007.pdf

2. Please provide response to all QbR questions and do not delete or alter any question. Please refer to OGD web site for complete list of QbR questions.
[http://www.fda.gov/cder/ogd/QbR_Summary_outline.htm]

3. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

4. Your labeling information is deficient. Please respond to the deficiencies.

5. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

6. Please provide any additional long term stability data that may be available.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Gururaj Bykadi
9/11/2007 10:32:40 AM

BIOEQUIVALENCY AMENDMENT

ANDA 78-502

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Cypress Pharmaceuticals, Inc. TEL: 800-856-4393

ATTN: Robert L. Lewis FAX: 601-853-1567

FROM: Steven Mazzella PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on October 16, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcium Acetate Tablets USP, 667 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

ANDA: 78-502

APPLICANT: Cypress Pharmaceutical,Inc.

DRUG PRODUCT: Calcium Acetate Tablets USP, 667mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified in the report of the in vitro binding BE study No. REP-06-022.

1. Your phosphate binding study procedure is not acceptable, because it is not designed for the determination of the phosphate precipitation capacity. You determined relative phosphate binding capacity (test/reference) by measuring the amount of calcium phosphate precipitate by gravimetric analysis and not by analyzing the free calcium and free phosphate in the supernatant once precipitation has occurred. In addition, your experiment was conducted using only one concentration of phosphate solution at one time point. To demonstrate bioequivalence using in vitro phosphate-binding capacity of the drug products (test vs. reference), you need to conduct an equilibrium experiment on the drug products that uses several concentrations (e.g., 0 to 5.6334 mMoles or higher) of phosphate solution at one incubation time point as described below.

2. Please repeat your in vitro phosphate binding study as **outlined** below:

   a. Prepare eight vessels for test and eight vessels for reference. Completely dissolve one calcium phosphate tablet or capsule in appropriate volume of deionized water.
   b. Add varying amounts of sodium phosphate (Na_3PO4) in the eight incubation vessels (e.g., 0.0, 0.02817, 0.14084, 0.28167, 1.12668, 1.97169, 2.8167 and 5.6334 mMoles). Please note higher than 5.6334 mMoles of sodium phosphate may be necessary to achieve complete phosphate precipitation capacity and a meaningful phosphate binding profile. Accordingly, more than 8 vessels for test and reference will be required.
   c. Incubate at 37°C in a shaking water bath until complete precipitation has occurred.
   d. Separate the supernatant using appropriate method, e.g., centrifugation or vacuum filtration.
   e. Measure the free calcium and free phosphate in the supernatant using validated analytical methods.
   f. Carry out the binding assay (steps a-e) on 12 replicates each for test and reference products.
   g. Present the data (mMole or mg) for calcium and phosphate (PO_4) in the supernatant in table format.
   h. The phosphate binding capacity (maximum binding) is determined from the mMoles (or mg) difference between Vessel 1 and Vessel 8 or more as the case may be).
   i. A plot of data from Vessels 1 through 8 (or more as the case may be) will provide the phosphate binding profile.
   j. Compare the mean of maximum binding for test to the mean of maximum binding for reference (T/R binding ratios). For binding capacity, the T/R ratio should fall within ±10% (0.9 to 1.1). Please also provide a 90% confidence interval (transferred and log-transformed data) of the maximum binding capacity of the test and reference. The DBE will set an interim specification upon review of the submitted results. The similarity factor (f2) may be used to compare the mean profiles for the test and reference products.

3. Please develop sensitive, specific and validated analytical methods for measuring phosphate and calcium. Please provide pre-study and during study data (including all concentrations of standards and QCs; precision, accuracy

and range) for Phosphate and Calcium analyses. Please provide bio-batch size and content uniformity for the test product. Please refer to the FDA guidance, Bioanalytical Method Validation (Issued 5/2001) for more information.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner

9/4/2007 01:46:52 PM

LABELING COMMENTS

ANDA 78-502

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8962)

TO: Cypress Pharmaceutical, Inc. TEL: 1800-856-4393

ATTN: Robert L. Lewis II FAX: 601-853-1567

FROM: Ruby Wu

Dear Sir:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcium Acetate Tablets USP, 667 mg (EQ 169 mg calcium).

Pages (including cover): __3__

SPECIAL INSTRUCTIONS:

Labeling comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-502
Date of Submission:	October 16, 2006 (original)
Applicant's Name:	Cypress Pharmaceutical, Inc.
Established Name:	Calcium Acetate Tablets USP, 667 mg (EQ 169 mg calcium)
Proposed Proprietary Name:	Eliphos Tablets

Labeling Deficiencies:

1. GENERAL COMMENT:
   Your proposed proprietary name "Eliphos" is under review. We will inform you of our comments when they become available. Please note that in the event that your application is approved after 90 days of the current submission then the name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. CONTAINER LABEL (Bottles of 200s)
   a. Ensure that the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
   b. Increase the prominence of the expression of strength.

3. PHYSICIAN INSERT:
   How supplied: Please include the product imprinting in the description of the tablets.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
6/18/2007 02:40:45 PM
for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 78-502 **FIRM NAME**: CYPRESS PHARMACEUTICALS INC.

PIV: NO **Electronic or Paper Submission:** ECTD FORMAT (ELECTRONIC DATA)

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: CALCIUM ACETATE
DOSAGE FORM: TABLETS USP, 667 MG
(EQ. 169 MG)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Random Queue: 5
Chem Team Leader: Bykadi, Raj PM: Ben Danso Labeling Reviewer: Ruby Wu

Letter Date: OCTOBER 16, 2006 **Received Date**: OCTOBER 17, 2006

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 3020400 BONE /CALCIUM –PHOSPHOROUS METABOLISM

Archival copy: ECTD FORMAT ELECTRONIC DATA **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category 9 Other Type of Part3 Combo Prod
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Kwadwo Awuah** **Date** **01/12/2007**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
Called Cypress Pharms on January 3, 2007, spoke to Robert Lewis and asked him to provide the following:
1. **A revised 356H form with the correct established name of the drug product**
2. **A revised Type 3 DMF authorization letter authoring the applicant instead of the contract manufacturer**

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Contact Person: William C. (Trey) Putnam Phone # (913) 451-3955** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES – Revised Version dated January 11, 2007	☒
1.2	**Cover Letter** Dated: OCTOBER 16, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) Y	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) NO (IN-VITRO STUDIES SUBMITTED)	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) Paragraph III Patent Certification to 4,870,105 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): 4-07-2007 a. Pediatric exclusivity submitted? NO b. Expiration of Pediatric Exclusivity? NA 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (DMF # (b) (4)) b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) - **Please send all communications here**	☒
1.12.11	**Basis for Submission – Citizens Petition dated 9/27/06** NDA# : 19-976 Ref Listed Drug: PHOSLO Firm: FRESENIUS MEDCL (USED TO BE NABI BIOPHARMACEUTICALS) ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as the RLD 2. Active ingredients Calcium Acetate 3. Inactive ingredients OK per IIG. IIG Checklist attached to this document. 4. Route of administration Oral 5. Dosage Form Tablets 6. Strength 667 mg (Eq to 169 mg Calcium)	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Electronic, YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? YES (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __X___PDF (archive) _X___ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _X____ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence) – Comparative Study Provided** **E-Submission: _X____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1 (See Section 5.3.1.2)** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** **3.2.S.1.2** **Structure** **3.2.S.1.3** **General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API (DMF # (b) (4)) 4. FEI numbers (b) (4)	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y (Contract Person) **3.2.S.4.5** **Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials - NA**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG – YES (IIG Checklist attached)	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) Y 2. CGMP Certification: YES 3. Function or Responsibility Y 4. CFN or FEI numbers Y **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Y 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation - NA** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☐
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** **3.2.P.4.3** **Validation of Analytical Procedures** **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form Y **3.2.P.5.5** **Characterization of Impurities** **3.2.P.5.6** **Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch **Y**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) - DMF** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation (ANDA BATCH # CP06005) Theoretical Yield (b) (4) tablets) Actual Yield (b) (4) tablets) Packaged Yield (b) (4) tablets **3.2.R.1.P.2** **Information on Components** **3.2.R.2.P** **Comparability Protocols** **3.2.R.3.P** **Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies – COMPARATIVE PHOSPHATE BINDING STUDY SUBMITTED OK AS PER Dr. Barbara Davit (Also look at Control Doc. No. 01-353)**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐
	5.3.1.2 **Comparative BA/BE Study Reports NA** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Y Table 5. Formulation Data Y **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☒

5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES) (**i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES) (**i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Fyi

----- Original Message -----
From: Boocker, Nancy
To: Catchings, Mary E
Cc: Parise, Cecelia M; Mueller, Nicole
Sent: Wed Jan 03 15:32:55 2007
Subject: RE: Citizens Petition for PhosLo (Calcium Acetate) Tablets - NDA 19-976 submitted by Beckloff Associates for Cypress Pharmaceuticals

Mary,

We have a couple relisting CPs for PhosLo. They are assigned to Nikki. I think there is a draft FR Notice that is on my desk.

Nancy

-----Original Message-----
From: Catchings, Mary E
Sent: Wednesday, January 03, 2007 3:18 PM
To: Boocker, Nancy
Subject: FW: Citizens Petition for PhosLo (Calcium Acetate) Tablets - NDA 19-976 submitted by Beckloff Associates for Cypress Pharmaceuticals

Nancy,

Do we have this CP?

Thanks,

Mary

-----Original Message-----
From: Parise, Cecelia M
Sent: Wednesday, January 03, 2007 3:14 PM
To: Catchings, Mary E
Subject: Fw: Citizens Petition for PhosLo (Calcium Acetate) Tablets - NDA 19-976 submitted by Beckloff Associates for Cypress Pharmaceuticals

Mary.

Do you have any info on this subject?

Cec

----- Original Message -----
From: Awuah, Kwadwo
To: Parise, Cecelia M
Sent: Wed Jan 03 14:42:49 2007
Subject: Citizens Petition for PhosLo (Calcium Acetate) Tablets - NDA 19-976 submitted by Beckloff Associates for Cypress Pharmaceuticals

Hello Cec, do you have any information regarding this CP? Cypress Pharmaceuticals recently submitted an ANDA citing NDA 19-976 (currently listed in the discontinued section of the OB) as their basis and they indicated that they had submitted a CP on 9/27/2006 inquiring whether the RLD was withdrawn for safety or efficacy reasons. The CP was submitted to FDA Dockets Management. Thanks for your help and have a good one.

Kojo

CYPRESS
PHARMACEUTICAL, INC.

January 11, 2007

Kwadwo Awuah, Pharm.D., R.Ph.
Project Manager, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Beltsville, MD 20855

Re: ELIPHOS™ Tablets (Calcium Acetate, USP)
ANDA No. 078-502
Revised Form FDA 356h and Revised DMF Letter of Authorization from (b) (4)

Amendment No. 001, NEW CORRESPONDENCE

Dr. Awuah:

Per your telephone request of January 3, 2007, please find enclosed a revised Form FDA 356h and revised DMF Letter of Authorization from (b) (4) for ELIPHOS™ Tablets (Calcium Acetate, USP) ANDA.

If there are any questions concerning this submission, please contact our agent at the following address:

Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Contact Person: William C. (Trey) Putnam, Ph.D.
Telephone: 913-451-3955
Facsimile: 913-451-3846

Sincerely,

Robert L. Lewis II
Director of Product Development
Cypress Pharmaceutical, Inc.

Enclosures

[illegible] 5 Industrial Blvd., Madison, MS 39110 • Mailing Address: P.O. Box 399, Madison, MS 39130
Phone: (601) 856-4393 • Fax: (601) 853-1567
www.cypressrx.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Cypress Pharmaceutical, Inc.	01/11/2007
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(800) 856-4393	(601) 853-1567
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 135 Industrial Blvd. Madison, MS 39110	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE** William C. (Trey) Putnam, Ph.D. Beckloff Associates, Inc. Commerce Plaza II, Suite 300 7400 West 110th Street Overland Park, KS 66210 Telephone: 913-451-3955 Facsimile: 913-451-3846

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* N/A

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Calcium Acetate Tablets, USP	ELIPHOS™ Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*		CODE NAME *(if any)*
Calcium Acetate		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablet	667 mg (eq. 169 mg calcium)	Oral

(PROPOSED) INDICATION(S) FOR USE:
Control of hyperphosphatemia in end stage renal failure

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug PhosLo Tablets (Calcium Acetate) Holder of Approved Application Nabi Biopharmaceuticals

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Submission of Revised Form FDA 356h and revised (b) (4) DMF Letter of Authorization

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 CD-ROM THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached Establishment List as Appendix 1

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF No.	(b) (4)
DMF No.	
DMF No.	
DMF No.	

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Revised Form FDA 356h and revised (b) (4) DMF Letter of Authorization

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Robert L. Lewis II, Director of Product Development	01/11/2007

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
135 Industrial Blvd., Madison, MS 39110	(800) 856-4393

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Appendix 1

Establishment Information

Manufacturing Step	Manufacturer Name and Address	Contact and Telephone No.	CFN or FEI No.	DMF No.	Ready for Inspection
				(b) (4)	Yes
					Yes
					Yes
					Yes
					Yes

NA = Not applicable

(b) (4)

January 9, 2007

Drug Master File Staff
Food and Drug Administration
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852

Dear Sir or Madam:

(b) (4) authorizes the following company to cite our Drug Master File # DMF- (b) (4) in support of a drug application in which the use of our (b) (4) is proposed:

CYPRESS PHARMACEUTICAL, INC.
135 INDUSTRIAL BLVD.
MADISON, MS 39110

Pertinent DMF Information:

Holder: (b) (4)
DMF Number:
Products Relevant:
Submission Date:
Applicable Sections:

(b) (4) Drug Master File is current, and we are committed to complying with the policies and procedures detailed therein. Should any amendments be needed, the Drug Master File will be updated accordingly and the above-mentioned customer will be so notified.

Please hold the information in DMF- (b) (4) as confidential to the FDA to the extent possible under 21 CFR Sections 314.430 and 20.61.

Sincerely yours,

(b) (4)

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

/s/

Iain Margand
6/5/2007 02:31:19 PM
Signing for Martin Shimer. Checklist not entered into DFS at the same time as Ack letter.