

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-160

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-160 / 1000</u> - _____	
Drug <u>PhosLo Capsules + Gels</u>	Applicant <u>Brain Tree Labs.</u>
RPM <u>R Hedlin</u>	Phone <u>301-927-6392</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>None</u>	
Application classifications: Chem Class <u>3S</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>April 3, 2001</u> Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information:
 - User Fee Paid
 - User Fee Waiver (attach waiver notification letter)
 - User Fee Exemption No clinical data

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... 3/29/01
 - Original proposed labeling (package insert, patient package insert) 6/3/99
 - Other labeling in class (most recent 3) or class labeling..... Has been reviewed
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels 6/3/99
 - Nomenclature review NA

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... NA
 - OC Clearance for approval..... NA

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter
- ◆ Post-marketing Commitments
 - Agency request for Phase 4 Commitments Relative Post Marketing Commitment
 - Copy of Applicant's commitments NA
- ◆ Was Press Office notified of action (for approval action only)? Yes No
- ◆ Patent
 - Information [505(b)(1)] X
 - Patent Certification [505(b)(2)] X
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] NA
- ◆ Exclusivity Summary X
- ◆ Debarment Statement No Clinical Trials
- ◆ Financial Disclosure
 - No disclosable information X
 - Disclosable information – indicate where review is located _____
- ◆ Correspondence/Memoranda/Faxes X
- ◆ Minutes of Meetings X
 - Date of EOP2 Meeting None
 - Date of pre NDA Meeting None
 - Date of pre-AP Safety Conference None
- ◆ Advisory Committee Meeting
 - Date of Meeting None
 - Questions considered by the committee NA
 - Minutes or 48-hour alert or pertinent section of transcript NA
- ◆ Federal Register Notices, DESI documents None

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) NA
- ◆ Clinical review(s) and memoranda NA

- ◆ Safety Update review(s) NA
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred
Pediatric Page.....
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda NA
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) NA
Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda NA
- ◆ DSI Audits NA
 Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability NA
- ◆ DMF review(s) NA
- ◆ Environmental Assessment review/FONSI/Categorical exemption X
- ◆ Micro (validation of sterilization) review(s) and memoranda NA
- ◆ Facilities Inspection (include EES report)
Date completed 2/22/00 Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) NA

- ◆ Statistical review(s) of carcinogenicity studies NA
- ◆ CAC/ECAC report NA

**APPEARS THIS WAY
ON ORIGINAL**

Number of Pages
Redacted 12



Draft Labeling
(not releasable)

LABORATORIES, INC
Braintree

March 8, 2000

Via Facsimile (301) 443-9282

Randy Hedin
Food and Drug Administration
Division of Endocrine Drug Products (HFD-510)
Document Control Room #14B-03
5600 Fishers Lane
Rockville, MD 20857

Re.: NDA 21-160; PhosLo Capsule and Gelcap

Dear Randy:

Please be advised that Braintree Laboratories owns a patent for the use of calcium acetate for the treatment of hyperphosphatemia. This is U.S. Patent No. 4870105.

If you have any questions, please call me or Mark Cleveland.

Sincerely,



Vivian A. Caballero
Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-160 SUPPL # _____

Trade Name PhosLo Caps & Gelcaps Generic Name Calcium Acetate

Applicant Name Braintree Laboratories HFD- 510

Approval Date April 2, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES/X/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /X/

If yes, what type (SE1, SE2, etc.)? _____

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

YES /___/ NO /X/

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

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

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /___/ NO / X /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

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

Investigation #1	!		
	!		
IND # _____	!	YES /___/	NO /___/ Explain: _____
	!		_____
	!		_____
	!		
Investigation #2	!		
	!		
IND # _____	!	YES /___/	NO /___/ Explain: _____
	!		_____
	!		_____
	!		

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

Investigation #1	!		
	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		
Investigation #2	!		
	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		

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

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title: _____

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD-510/Division File
HFD-510/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Randy Hedin
4/2/01 05:44:49 AM

David Orloff
4/2/01 08:52:18 AM

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ON ORIGINAL**

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

[View as Word Document](#)

NDA Number: 021160 **Trade Name:** PHOSLO(CALCIUM ACETATE)667MG/333.5MG CAP
Supplement Number: 000 **Generic Name:** CALCIUM ACETATE CAPSULES/GELCAPS 667+333
Supplement Type: N **Dosage Form:**
Regulatory Action: AE **COMIS Indication:** CONTROL OF HYPERPHOSPHATEMIA IN END STAGE RENAL FAILURE PATIENTS
Action Date: 4/4/00

Indication # 1 The control of hyperphosphatemia in end stage renal failure.
Label Adequacy: Inadequate for ALL pediatric age groups
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any): This application provides two new dosage forms, Gelcaps and Capsules. 4/3/01

Ranges for This Indication

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	Adult	Deferred	

This page was last edited on 4/3/01


 Signature

4/3/01
 Date

**APPEARS THIS WAY
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TEAM LEADER MEMO
SUPPLEMENTAL NDA

NDA#: 21-160

DRUG: PhosLo (calcium acetate)

INDICATION: Control of hyperphosphatemia in end stage renal disease

SPONSOR: Braintree Laboratories

DATE SUBMITTED: June 3, 1999

PRIMARY MEDICAL REVIEWER: Leo Lutwak

DATE OF MEMO: March 30, 2000

PhosLo is approved for the control of hyperphosphatemia in end stage renal disease. The tablet is the only currently approved formulation. This supplemental application contains no clinical data. The Sponsor is seeking approval of new dosage forms – a capsule and a caplet. The primary reviews therefore reside with Biopharm and Chemistry.

Based on dissolution tests and in vitro phosphate binding studies, the Biopharmaceutics reviewer has concluded that the capsules are equivalent to the tablets. However, because of inadequate dissolution methodology, the caplets cannot be considered equivalent to the tablets.

A question has been raised about the labeling. In the How Supplied section, but not the Dosage and Administration section, the tablet formulation is mentioned. This is not unusual for labels of drugs with multiple formulations and does not require any changes.

In his memo, Dr. Lutwak mentions that the label implies equivalence of the tablet and the capsule, but he could not find data to support this. The dissolution and in vitro binding data are the basis for the Biopharmaceutical reviewer's conclusion that the tablet and capsule are equivalent. The tablet and caplet formulations are not considered equivalent at this time.

Comment

This supplement contains no clinical data and therefore decisions regarding approvability will come from the Biopharmaceutical and Chemistry reviewers. Both of these disciplines have pointed out deficiencies that need to be addressed prior to approval of this application.

From a clinical standpoint, the Sponsor should be informed that the labeling needs to conform to the requirements defined in the final rule regarding the Geriatric Use Subsection.

IS/
Eric Colman, MD *3/31/00*

cc: NDA Arch

*No clinical
concern*
IS/ *IS/*

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: _____ DMF No:
_____ AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

**APPEARS THIS WAY
ON ORIGINAL**

**Number of Pages
Redacted** 7



Confidential,
Commercial Information

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: _____ **DMF No:**
_____ **AADA No:**

Profile: CTL **OAI Status: NONE** **Responsibilities:** _____
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-DEC-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**APPEARS THIS WAY
ON ORIGINAL**

D. ENVIRONMENTAL ASSESSMENT: (Vol.1.1, pp. 153) [Satisfactory]

A satisfactory Categorical Exclusion under 21 CFR25.31(a) was provided. The capsule and gelcap versions will be substituted for the tablets. Thus, there will be no anticipated increase in the use of the active ingredient.

E. METHODS VALIDATION: (Satisfactory)

Since the formulation and the methods used to monitor the specifications of the drug products are the same for PhosLo capsules, gelcaps, and tablets no Methods Validation Package will be requested.

F. LABELING: [Vol. 1.1 & Vol. 2.1 (sections before pp. 001)
[Not satisfactory]

The PhosLo products (bottles of capsules and gelcaps) are not packaged in cartons. The package insert is attached to the bottle label in such a way so that the prescribing information (etc.) can be torn away from the bottle label for convenient reading.

The following deficiency was found in the labeling:

Since the labeling for NDA 19-976 describes the product as PhosLo (Calcium Acetate Tablets), the name "PhosLo" now stands only for calcium acetate tablets and can not be used for capsules or gelcaps. If Braintree Laboratories wishes to retain the name "PhosLo" for all three dosage forms, the applicant may label the products as follows"

PhosLo Capsules
(Calcium Acetate)

PhosLo Gelcaps
(Calcium Acetate)

In this scenario, NDA 19-976 should be amended to make the name change; and reference to the _____ in the "How Supplied " sections for PhosLo capsules and PhosLo gelcaps should be eliminated.

**APPEARS THIS WAY
ON ORIGINAL**

Electronic Mail Message

NDA 21-160

Date: 3/20/00 10:42
From: Randy Hedin
To: Eric Colman (COLMANE)
To: Leo Lutwak (LUTWAKL)
To: Sheldon Markofsky (MARKOFKYS)
To: Duu Gong Wu (WUD)
Subject: Memo on PhosLo HOW SUPPLIED section

Hi,

I spoke with Braintree Labs. about the HOW SUPPLIED section of the PhosLo Gelcap label and why they mention the tablet in the HOW SUPPLIED section and not in other parts of the label. She stated that they have different labels for gelcaps and tablets, and in the tablet label, gelcaps aren't mentioned. She stated that she would research how other manufacturers handle this issue, and send me a letter justifying the way they do it, or change the label.

Thanks,

Randy

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cc: NDA Arch
HFD-510/EColman/LLutwak/SMarkofsky/DWu
HFD-511/RHedin/3.20.00/N21160_PH1.doc

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TELEFAX

To: Mr. Mark Cleveland
Braintree Laboratories

FAX: 781-843-7932
PHONE: 781-843-2202

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: August 20, 1999

Pages: 2 [inclusive]

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TELEFAX

To: Mr. Mark Cleveland
Braintree Laboratories

FAX: 781-843-7932
PHONE: 781-843-2202

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: August 20, 1999

Pages: 2 [inclusive]

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Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

NDA 21-160
PhosLo

Dear Mr. Cleveland:

Please refer to your pending June 3, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PhosLo.

We are reviewing the biopharm section of your submission and have the following comments:

The dissolution testing for the approved tablets, gelcaps and capsules should be carried out in 5 different media in paddles at 50 rpm at 15 minute intervals to generate dissolution profiles using 12 dosage units. For a rapidly dissolving product, generation of an adequate profile sampling at 5- or 10-minute intervals may be necessary. Then, similarity factors (f_2) should be calculated between the approved tablets and gelcaps, and the approved tablets and capsules in each dissolution medium.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,



Dr. Hae-Young Ahn
Team Leader, OCPB/DPE-2 for the
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

N21160_Fax1.doc

NDA 21-160
NDA 19-976

JUL 27 1999

Braintree Laboratories, Inc.
Attention: Mark Cleveland
Vice President, New Product Development
60 Columbia Street
P.O. Box 850929
Braintree, MA 02185-0929

Dear Mr. Cleveland:

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

Name of Drug Product:	PhosLo (calcium acetate) Capsules, 667 mg , 333.5 mg, and PhosLo (calcium acetate) Gelcaps, 667 mg
Review Priority Classification:	Standard (S)
Date of Application:	June 3, 1999
Date of Receipt:	June 4, 1999
Our Reference Number:	NDA 21-160

Your submission of a supplemental new drug applications for a new capsule dosage form and new gelcap dosage form was unbundled from your approved NDA according to the Center for Drug Evaluation and Research guidance ("bundling policy"- enclosed) which states that different dosage forms are to be submitted in separate, original new drug applications. Based on our review of your submissions and our telephone discussions, we have determined that the new capsule products meet the criteria for a new dosage form and thus a new NDA was created. For purposes of this "bundling policy", your immediate release gelcap and immediate release capsules are treated as one new dosage form; i.e., capsules.

Payment of a user fee is now due for an original new application without clinical data. A check for the appropriate fee should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and unique user fee identification number is on the enclosed check.

Also, please submit a cover letter, Form FDA 356h, and a new User Fee Cover Sheet (Form FDA 3397) with a unique user fee identification number to this new NDA at the address listed below.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, the application will be filed under section 505(b) of the Act on August 3, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 4, 2000, and the secondary user fee goal date will be June 4, 2000.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric

Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

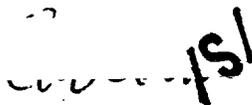
Please cite the new NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Randy Hedin, Regulatory Project Manager, at 301-827-6392.

Sincerely yours,


Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

**APPEARS THIS WAY
ON ORIGINAL**

cc:

Archival NDA 21-160

Arch. NDA 19-976

HFD-510/Div. Files (2)

HFD-510/CPMS

HFD-510/CSO-Hedin

HFD-510/DWu/SMarkofsky

HFD-510/HAhn

DISTRICT OFFICE

Drafted by:emg/7.9.99; Edited by emg/7.27.99/

filename:c:\wpfiles\21160ac.unb

FT/emg/7/27/99

ACKNOWLEDGEMENT (AC)

Remove S-006 from NDA 19-976 and re-jacket it as NDA 21-160, volume 1.1

Remove S-005 from NDA 19-976 and re-jacket it as NDA 21-160, volume 2.1

Delete all entries for N 19-976/S-005 and S-006 from COMIS, ECH, and paper C + H

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Date: March 14, 2000 Time: 1:30 - 2:10 am Location: 14-56

NDA 21-160 PhosLo

Type of Meeting: Status Meeting

External participant: None

Meeting Chair: Dr. Eric Colman

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Eric Colman, Medical Team Leader, DMEDP
Dr. Leo Lutwak, Medical Reviewer DMEDP
Dr. Shelly Markofsky, Chemistry Reviewer, DNDCII
Dr. Duu-Gong Wu, Chemistry Team Leader, DNDCII
Dr. Hae-Young Ahn, Team Leader OCPB
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

Internal meeting requested by the project manager to discuss the status of the reviews of PhosLo, and any labeling issues.

Discussion Points and Decisions (agreements) reached:

Biopharm: The review is finished and it is approvable. The new caplets can not be considered equivalent to the PhosLo tablets at this time. In order to support approval for the caplets, acceptable dissolution tests using 12 dosage units should be conducted in 5 different dissolution media with a paddle speed of 50 rpm. The firm was informed that it needed to do this test in August. This information has not been submitted.

Chemistry: The chemistry review is not complete. The chemistry team leader feels it will be done by the end of next week. The review will include minor deficiencies that need to be conveyed to the firm. Also, there is some concern with stability issues.

Clinical: There are no clinical issues, and the review is with the medical team leader. There is one issue with the label. The tablet dosage form is only mentioned in the **HOW SUPPLIED** section, not in the **DOSAGE AND ADMINISTRATION**, or under the **DESCRIPTION** sections. The firm should explain why.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Issue an approvable letter when the reviews are complete.

Signature, minutes preparer: _____

IS/

Concurrence Chair: _____

IS/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/3.15.00/N21160.MN1
Concurrences: LLutwak/EColman/SMarkofsky/DWu/HAhn/3.16.00

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Date: August 2, 1999 Time: 11:30 - 12:15 PM Location: 14-56

NDA 21-160 PhosLo Capsules

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Sobel

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director DMEDP
Dr. Leo Lutwak, Medical Reviewer DMEDP
Dr. Sheldon Markofsky, Chemistry Reviewer, DNDCII
Dr. Hae-Young Ahn, Team Leader, OCPB
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-160 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

Chemistry: The application is fileable. However, there are review issues. The firm has submitted information on only one batch of product to determine stability. Three batches for each formulation are required.

Biopharmaceutics: The application is fileable. However, more dissolution testing will be required.

Clinical: The application is fileable.

Decisions (agreements) reached:

- The application will be filed.
- The review will be done as a standard review. The goal to finish the reviews will be March 4, 2000.
- A labeling meeting will be scheduled to be held the end of March 10, 2000.
- There will be no DSI inspections, and there will not be an Advisory Committee meeting.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, minutes preparer: _____

JSI

Concurrence Chair: _____

JSI

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/9.10.99/N21160.MN1
Concurrences: LLutwak/9.10/SMarkofsky/9.13/HAhn/9.20.99

Meeting Date: August 2, 1999 Time: 11:30 - 12:15 PM Location: 14-56

NDA 21-160 PhosLo Capsules

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Sobel

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director DMEDP
Dr. Leo Lutwak, Medical Reviewer DMEDP
Dr. Sheldon Markofsky, Chemistry Reviewer, DNDCII
Dr. Hae-Young Ahn, Team Leader, OCPB
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-160 will be filed, and discuss plans for the review of the NDA.

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Biopharmaceutics: The application is fileable. However, more dissolution testing will be required.

Clinical: The application is fileable.

Decisions (agreements) reached: