

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205109Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Memorandum

Date: November 27, 2013

Reviewer: Jean Olumba, MD, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Julie Neshiewat, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Velphoro (Sucroferric Oxyhydroxide) Chewable Tablets,
500 mg

Application Type/Number: NDA 205109

Applicant: Vifor Inc.

OSE RCM #: 2013-684

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

1 INTRODUCTION

This memorandum evaluates the revised labels and labeling for Velphoro (Sucroferric Oxyhydroxide) Chewable Tablets, NDA 205109, submitted on November 27, 2013 (Appendices A and B). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-684 dated October 5, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling submitted on November 27, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-554 dated October 5, 2013 and the recommendations sent via e-mail to the Applicant on November 22, 2013 and November 25, 2013.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager: Karen Bengtson, at 301-796-3338.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

JEAN C OLUMBA
11/27/2013

JULIE V NESHIEWAT
11/27/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 22, 2013

To: Anna Park, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 205109**
OPDP Labeling Comments for Velphoro (sucroferric oxyhydroxide) chewable tablets for oral use

OPDP has reviewed the proposed carton and container labeling and Package Insert (PI) submitted for consult on March 20, 2013, for Velphoro (sucroferric oxyhydroxide) chewable tablets for oral use.

Our comments on the carton and container labeling are based on the proposed labeling emailed to us on November 22, 2013. OPDP has no comments on the proposed carton and container labeling at this time.

Our comments on the PI are based on the proposed labeling emailed to us on November 21, 2013. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed materials.

If you have any questions, please contact Emily Baker at 301.796.7524 or Emily.Baker@fda.hhs.gov.

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

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/s/

EMILY K BAKER
11/22/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	Velphoro (sucroferic oxyhydroxide) chewable tablet for oral use
Applicant	Fresenius Medical Care Renal Pharma France
Application/Supplement Number	NDA 205109
Type of Application	Original
Indication(s)	control of serum phosphorus levels in patients with chronic kidney disease on dialysis
Office/Division	ODE I/DCRP
Division Project Manager	Anna Park
Date FDA Received Application	February 1, 2013
Goal Date	December 1, 2013
Date PI Received by SEALD	November 22, 2013
SEALD Review Date	November 22, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *The horizontal line is missing between the TOC and the FPI.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment: The reference is missing after "None" in Contraindications; there seems to be a formatting glitch.

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The name of drug product is currently in title case and should be in upper case: VELPHORO.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: The year is missing and should read: "2013"

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The name of the manufacturer and toll-free phone number are missing.*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The date should reflect the approval date of this application and currently states: 10/2013. This should be revised when the approval date is known.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: *The heading for subsection 5.1 in the TOC does not match the FPI. The headings for subsections 14.1, 14.2 in the TOC do not match those in the FPI; recommend revising the headings in TOC with wording used in the FPI.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: *In subsection 8.3 and Section 10, Pharmacokinetics is cross-referenced where the correct cross reference would be: [see Clinical Pharmacology (12.3)]. In subsection 14.1, Adverse Reactions (6) is cross-referenced where (6.1) would likely be more appropriate. Also, in 17.1, prescribers are directed to DI (7); consider revising to include specific wording to prescribers, if applicable, regarding important information for prescribers to share with patients and provide a separate cross-reference to more detailed information in the FPI, if needed.*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is

Selected Requirements of Prescribing Information

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH A DONOHOE
11/22/2013

ERIC R BRODSKY
11/22/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
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INDUSTRY MEETING CONSULT MEMORANDUM

Date of Consult Request: June 4, 2013
Internal Meeting Date: August 28, 2013
Industry Meeting Date: September 12, 2013

From: Erica L. Wynn M.D., M.P.H, Medical Officer

Through: Hari Cheryl Sachs M.D., Team Leader
Lynne Yao M.D., OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: Division of Cardiovascular and Renal Products (DCaRP)

NDA Number: 205109
Product Name and Dose: PA 21 500mg chewable tablet
Active Pharmaceutical Ingredient: (b) (4)
Proposed trade name (b) (4) Velphoro
Associated IND 075610

Sponsor: Vifor Fresenius Medical Care Renal Pharma France (VFMCRP)

Proposed Indication: "Control of serum phosphorus levels in patients with (b) (4)
(b) (4)

Consult Request: Review and provide comment on the applicant's pediatric study plan outline. Participate in internal and industry meetings with the sponsor regarding the pediatric program.

Materials Reviewed:

- 1) Sponsor's meeting request dated June 17, 2013
- 2) DCaRP request for consultation dated June 4, 2013

- 3) Industry meeting background package submitted August 13, 2013
- 4) FDA Guidance for Industry : How to Comply with PREA
- 5) FDA Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Study Plans.
- 6) European Medicines Agency decision for Iron (III)-oxyhydroxide issued December 21, 2011.
- 7) Sponsor's Meeting Request dated August 13, 2010 submitted to IND 075610
- 8) DCaRP consult request dated August 18, 2010 for IND 075610.
- 9) PMHS Consult Review for IND 075610 by Dr. Virginia E. Elgin dated February 15, 2011.
- 10) Module 1.9 Sponsor's original NDA submission dated January 31, 2013

Background

Patients with chronic kidney disease experience biochemical abnormalities in calcium, phosphorus, parathyroid hormone, and vitamin D metabolism.¹ Consequently, these patients may also experience changes in bone histology as well as linear growth and fractures or vascular or other soft tissue calcifications.¹ "As renal function declines in chronic kidney disease, urinary phosphate excretion diminishes."² Studies have shown that elevated serum phosphate adversely affects carotid artery intima-media thickness, vascular stiffness, coronary calcifications and left ventricular mass.² Hyperphosphatemia is associated with increased mortality in adult patients with chronic kidney disease who are and are not dialysis-dependent.² The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommends that serum phosphorus levels be controlled and that phosphate levels do not exceed 5.5mg/dl in adults.^{3,4} Oral phosphate binders are designed to decrease dietary phosphate absorption, reduce serum phosphorus concentrations and minimize the risk for soft-tissue calcification and bone disease.⁴ A number of phosphate-binding agents are available; however, limitations of phosphate binder usage include the need for frequent pill ingestion, excessive calcium load resulting in increased risk of vascular calcification and other risks associated with hypercalcemia, gastrointestinal side effects, and altered bone mineralization.⁵

In January, 2013, the sponsor, Vifor Fresenius Medical Care Renal Pharma (VFMCRP), submitted an original New Drug Application (NDA) for PA 21 (b) (4) chewable tablet, 500mg (hereafter referred to as PA21). PA21 is an iron-based phosphate binder designed for therapeutic use in the control of serum phosphorus levels in patients with end-stage renal disease (ESRD). PA21 is a dry powder formulation of polynuclear iron(III)-oxyhydroxide, starch, and sucrose. The drug product is available as a chewable tablet with a content of approximately 2.5gm of PA21, adjusted to 500 mg iron. Per the sponsor, the active component (polynuclear iron(III)-oxyhydroxide) is practically insoluble and not absorbed. The iron oxide binds phosphate in the

gastrointestinal tract and prevents phosphorus absorption. Given the additional carbohydrate and limited absorption, the drug product is purported to maintain phosphate-binding capacity while avoiding the hypercalcemia associated with calcium-based products. There are no phosphate binders approved for pediatric use in the United States. Appendix B of this review provides information on the PREA requirements and Written Requests issued for related phosphate binder products that were approved for use in adults in the U.S.

In August 2010, the sponsor's U.S. agent submitted a request for a Type C meeting to discuss the adequacy of the pediatric development plan for PA21. At that time, the sponsor (b) (4) proposed to submit with the NDA, a deferral request to conduct an open-label, randomized, active-controlled, parallel group Phase 3 trial to assess the safety and efficacy of PA21 (b) (4)

The sponsor also planned to submit a waiver to conduct pediatric trials in patients less than one year of age on the grounds that PA21 (b) (4) necessary studies are impossible or highly impracticable because the number of patients in that age group on dialysis is small. The Agency requested that the sponsor provide additional data to support their plan to request a (b) (4) waiver in pediatric patients less than 1 year of age. The Agency also recommended that pediatric studies be delayed until after the safety and effectiveness of PA21 was established in the adult population and age-appropriate formulations were available.

(b) (4)

Notably, the PDCO granted a waiver for pediatric patients from birth to less than 28 days of age (b) (4)

In a general advice letter sent to the sponsor on April 23, 2013, the FDA advised that the sponsor would need to submit a pediatric plan (b) (4)

In response to the advice letter, the

sponsor submitted a pediatric study outline for an active controlled (calcium acetate oral solution) Phase 4 study to be conducted in 3 stages in approximately 100 pediatric patients ≥ 28 days to ≤ 18 years of age with hyperphosphatemia secondary to chronic kidney disease. To be included in the trial, study subjects had to have been diagnosed for at least 1 year with Chronic Kidney Disease (CKD) Stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m²) or CKD Stage 5D receiving adequate maintenance hemodialysis (HD) or peritoneal dialysis (PD) for at least (b) (4) months prior to screening. Peritoneal dialysis subjects must have had 1 month of unchanged PD prescription (volume and number of exchanges). Stage 1 of the study is an open-label active controlled study with both fixed dose and dose-titration phases. Patients receive either PA21, Phoslyra (calcium acetate oral solution), or placebo. Stage 2 is a double-blind, randomized comparison of a PA21 fixed maintenance dose versus placebo for 3 weeks. Stage 3 is a 24-week open-label long-term safety extension. The sponsor proposes pre-defined stopping rules and the use of an external Data and Safety Monitoring Board. The sponsor states that (b) (4)



In June, 2013, the sponsor requested a face-to-face meeting with the FDA to discuss their global pediatric development plan in hopes of achieving harmonization between regions where possible. The background package for this meeting was submitted August 13, 2013, and DCaRP has requested the assistance of PMHS in reviewing the background package.

Summary of the Current Submission

The sponsor is currently developing a pediatric protocol [REDACTED] (b) (4)

- [REDACTED] (b) (4) PA21 chewable tablet (500mg iron)
- [REDACTED] (b) (4)

The active comparator is Phoslyra (calcium acetate oral solution), a phosphate binder approved in the U.S. for use in adult patients with End Stage Renal Disease. According to the prescribing information, the safety and efficacy of the Phoslyra product in pediatric patients have not been established. (Additional information related to Phoslyra is to follow.)

The sponsor is proposing to conduct a single, Phase 3 pediatric clinical trial, Study PA-CL-PED-01, in order to evaluate the efficacy and safety of PA 21 in the maintenance of lowering serum phosphorus in pediatric patients with chronic kidney disease. This study is part of the pediatric investigation plan approved by the EMA/PDCO. Pediatric patients 28 days to 18 years will be eligible for inclusion. Approximately 100 subjects will be randomized to treatment with PA21 and 30 subjects will be randomized to treatment with the active comparator (Phoslyra). A minimum number of subjects will be randomized to prespecified age groups. Major inclusion criteria for study participation are:

- Subjects with hyperphosphataemia i.e., with serum phosphorus levels as follows:

Age	mmol/L	mg/dL
≥28 days to <6 months	>2.62	>8.1
≥6 months to <1 year	>2.29	>7.1
≥1 year to <6 years	>2.02	>6.25
≥6 years to <13 years	>1.77	>5.53
≥13 years to <18 years	>1.36	>4.2

Note: Adapted from NKF KDOQI Nutrition Guidelines, 2008 and personal communication.

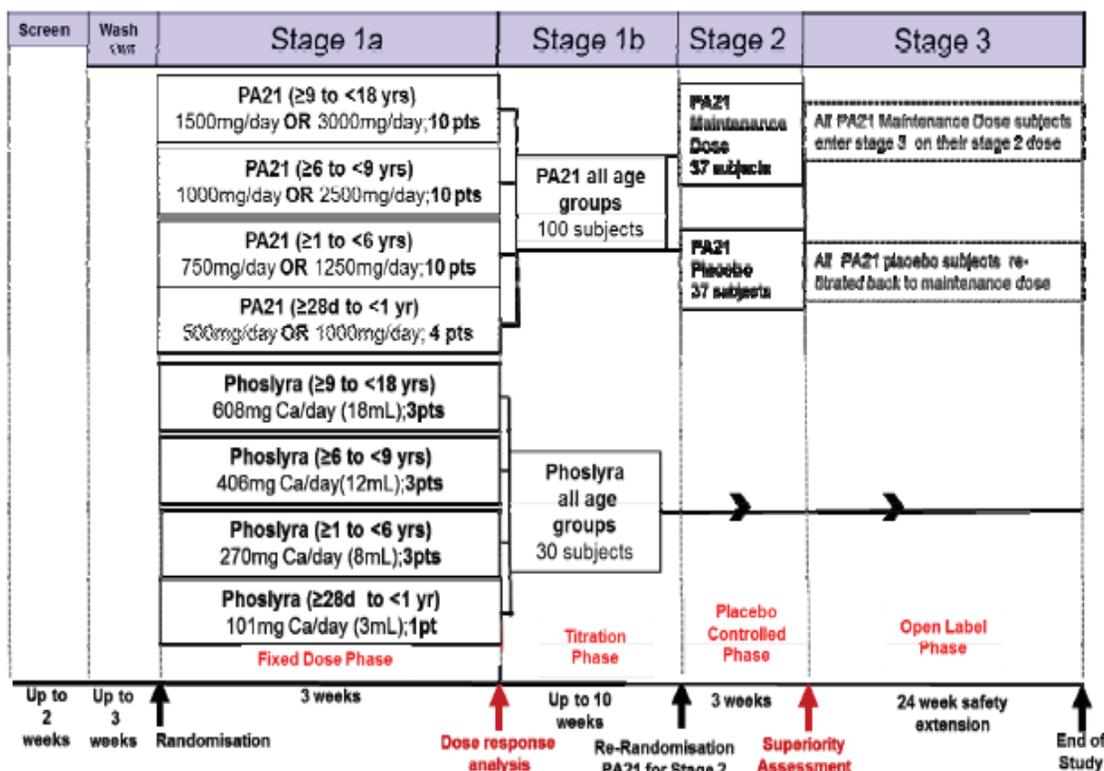
-
- Subjects who are phosphate binder (PB) naïve or have been receiving stable doses of PB(s) for at least 1 month prior to screening. Subjects may be on stable doses of a maximum of 2 PBs. Subjects who have been receiving PBs will enter an obligatory washout period and may be randomized once their serum phosphorus levels are as indicated in the table above. Subjects already receiving a PB but with serum phosphorus levels as indicated in table above may be eligible for randomization without a washout period.
- Subjects at least 1 year of age with CKD Stages 4-5 defined by a glomerular filtration rate of <30 mL/min/1.73 m² or with CKD Stage 5D receiving adequate maintenance hemodialysis (HD) or peritoneal dialysis (PD) for at least 2 months prior to screening. PD subjects must have had 1 month of unchanged PD prescription (volume and number of exchanges). Subjects ≤1 year of age with HP who have CKD or are on dialysis. Home HD subjects may be included. No nocturnal HD (overnight stay at site) will be allowed.

Major exclusion criteria for study participation are:

- Subjects with hypercalcemia at screening.
- Subjects with intact parathyroid hormone (iPTH) levels >700 pg/mL at screening
- Subjects with history of:
 - Major gastrointestinal surgery which, in the Investigator’s opinion, is likely to influence the outcome of treatment with phosphate binders
 - Significant gastrointestinal disorders
- Subjects with a history of hemochromatosis or other iron accumulation disturbances that might lead to iron overload.
- Subjects on PD with a history of peritonitis in the last 2 months or ≥3 episodes in the last 12 months.
- Subjects with hypocalcaemia (serum total calcium <1.9 mmol/L; <7.6 mg/dL) at screening.
- Subjects with raised alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of the normal range based on central laboratory results at screening.
- Subjects taking more than 2 PBs concomitantly prior to screening.
- Subject has initiated treatment with growth hormone within 1 month prior to screening or is expected to initiate treatment with growth hormone during the study.

The following figure (reproduced from the sponsor’s submission) provides an overview of the study design.

Figure 1: Summary of Study PA-CL-PED-01



Source: Sponsor’s Submission dated August 13, 2013 Figure 1 Module 1.6.2.1 page 37

Stage 1a is an open-label fixed dose comparison of PA21 with Phoslyra. Stage 1b will last up to 10-

weeks and is an open label, dose titration comparison of PA21 with Phoslyra. Subjects who achieve age specific target serum phosphorus levels on 2 consecutive visits will move to Stage 2, a 3-week double-blind comparison of PA21 fixed maintenance dose versus placebo. Stage 3 is an open label safety extension.

Starting doses in the pediatric study are based on the estimated phosphate bound per day, derived from Kidney Disease Outcomes Quality Initiative nutrition guidelines for children with chronic kidney disease and the results of Phase 2 and Phase 3 adult studies with PA21. Subjects in Stage 1a will be stratified based on their age to 1 of 2 doses. A dose titration schedule is used in Stages 1b and 3. Doses may be titrated for efficacy, safety, or tolerability reasons. Blood samples will be taken to obtain serum phosphorus levels for dose titration purposes. Target serum phosphorus levels are outlined in the table below reproduced from the sponsor's submission.

Table 1: Age-Related Targeted Serum Phosphorus Levels

Age	mmol/L	mg/dL
≥28 days to <1 year	1.62-2.52	5.0-7.8
≥1 year to <6 years	1.45-2.10	4.5-6.5
≥6 years to <13 years	1.16-1.87	3.6-5.8
≥13 years to <18 years	0.74-1.45	2.3-4.5

Note: Based on NKF K/DOQI Clinical Practice Guideline for Nutrition, 2008.

Source: Table 20 Sponsor's submission Module 1.6 2 1 page 39.

The primary endpoint will be change in serum phosphorus levels from baseline during the placebo-controlled stage of the study. This endpoint was used as the primary efficacy endpoint in the PA21 adult studies. There is no plan for conducting a responder analysis.

Reviewer Discussion

The sponsor has submitted their proposal for the pediatric program for PA21, a newly developed oral phosphate binder that will be used therapeutically to control the serum phosphorus levels in patients with end-stage renal disease. Renal osteodystrophy, a disorder of bone remodeling, is a common complication of chronic kidney disease.⁶ Treatment of hyperphosphatemia and secondary hyperparathyroidism that occurs as a result of chronic kidney disease is important for the appropriate development of the skeletal and cardiovascular systems of the developing child.¹ Oral phosphate binders have been used for a number of years to control serum phosphate levels; however, the role of phosphate control in determining patient outcomes must still be fully quantified and characterized.⁷ Longitudinal studies are needed to evaluate the effects of controlling serum phosphorus (within the target range) on morbidity and mortality.

Initially, dietary restriction is used in the management of phosphorus levels in patients with chronic kidney disease. If dietary measures fail, treatment with oral phosphate binders are recommended. Currently available oral phosphate binders work in a similar manner by binding phosphate in the gastrointestinal tract, either by forming an insoluble complex or by binding phosphate into a resin.⁷ Consequently, less phosphate is available to be absorbed and more phosphate passes through the gastrointestinal tract to be excreted in the feces.⁷

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) provides clinical practice guidelines for all stages of chronic kidney disease and related complications.⁶ A review of the literature reveals that there are gaps in the available database and therefore some aspects of the NKF guidelines are based upon opinion and experience of experts working in the field. NKF guidelines state that in patients with chronic kidney disease (Stages 1 -4) the serum level of phosphorus should be maintained at the age-appropriate limit and no higher than the age-appropriate upper limits.⁸ For adolescent children with stage 5 chronic kidney failure, including those treated with hemodialysis and peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 – 5.5 mg/dL (1.13 – 1.78 mmol/L) and between 4 -6 mg/dL for children between ages 1 – 12 years.⁸ Representative normal values for serum phosphate, calcium, and alkaline phosphatase are provided in the table below:

Representative Normal Values for Serum Phosphorus, Total Calcium, Blood Ionized Calcium, and Alkaline Phosphatase Concentrations

Age (yrs.)	Serum Phosphorus (mg/dL)	Serum Total Calcium (mg/dL)	Blood Ionized Calcium (mM)	Alkaline Phosphatase (IU)
0-0.25	4.8-7.4	8.8-11.3	1.22-1.40	
1-5	4.5-6.5	9.4-10.8	1.22-1.32	100-350
6-12	3.6-5.8	9.4-10.3	1.15-1.32	60-450
13-20	2.3-4.5	8.8-10.2	1.12-1.30	40-180

Source: Table 6 K/DOQI Workgroup. "K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease." American Journal of Kidney Diseases. 2005.46(4:1) page 28.

The Appendix of this review contains a table with a list of phosphorus binding compounds, none of which are approved in pediatric patients. Aluminum salts have been used since the 1970s. However, these products have been associated with cognitive disturbances, osteomalacia, and anemia.⁷ Because long-term use of aluminum containing phosphate binders have been associated with bone disease and encephalopathy, only short-term courses (4-6) weeks are recommended for usage to control hyperphosphatemia.⁸

Lanthanum and sevelamer are also available for use as phosphate binders in adults. Lanthanum carbonate binds phosphate efficiently at lower pH concentrations and has low potential for accumulation. Consequently, the drug has less potential to cause systemic drug-drug interactions. Per product labeling, use in pediatric patients is not recommended because lanthanum was deposited into developing bone in juvenile animal studies. Sevelamer is a nonselective anion exchanger that has been demonstrated to be effective in maintaining control of serum phosphate levels in adults. However, sevelamer also has the potential to bind lipophilic drugs, such as immunosuppressants.⁷ Cases of fecal impaction, including bowel obstruction and perforation have also been reported (product labeling). Notably, the sponsors for sevelamer carbonate received a noncompliance letter on April 11, 2013, for failure to submit PREA-required pediatric assessments to the FDA.

(Noncompliance letters available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm>.)

NKF guidelines for use of phosphate binders in chronic kidney disease state that in patients with stages 2 – 4 chronic kidney disease, if serum phosphorus levels cannot be controlled within the target range, despite dietary phosphorus restrictions, phosphate binders should be prescribed.⁸ The guidelines also state that calcium-based phosphate binders such as calcium carbonate and calcium acetate are effective in lowering serum phosphorus levels and should be used as the initial binder therapy in both adults and children.⁸ Both calcium-based phosphate binders and the non-calcium, non-metal-containing phosphate binders, such as sevelamer HCL, are effective in lowering serum phosphorus levels in adults.⁸ As of 2005, NKF recommend that calcium-based phosphate binders should be used as primary therapy in infants and young children.⁸ The general opinion from the NKF is that in older children and adolescents, either calcium-based or non-metal based phosphate binders may be used.⁸ Furthermore, a combination of phosphate binders may be used to control serum phosphorus levels to minimize the potentially serious side-effects of any specific binder.

The sponsor proposed to use Phoslyra as an active comparator in the proposed pediatric plan. The sponsor of PA 21 also holds marketing rights for Phoslyra. Phoslyra is a calcium acetate oral solution approved for usage (NDA 022581) in the U.S. in adult patients with end stage renal disease in 2011. Safety and effectiveness of Phoslyra in pediatric patients have not been established. Because orphan drug status applied to the product for this indication, PREA was not triggered and the sponsor was not required to conduct pediatric trials. However, there were safety issues with use of the product that needed to be resolved, including the need for drug –drug interaction studies. Thus, there is an outstanding post-marketing commitment related to pediatrics for Phoslyra that is scheduled for completion by March 31, 2014:

- A multi-phase clinical trial in a hyperphosphatemic pediatric dialysis population, with a placebo-controlled dose-response phase, followed by an open-label titration and maintenance phase, followed by a placebo-controlled randomized withdrawal phase.

Because Phoslyra is not approved for usage in pediatric patients in the U.S., establishing a pre-specified non-inferiority margin between the PA21 and Phoslyra to support approval is not possible. However, because the sponsor has proposed a three-arm trial, the trial could be powered for both active treatment arms to show superiority over placebo. This may permit the Agency to gather the additional safety and efficacy data needed in pediatrics for the Phoslyra product. Alternatively, if the Division determines that extrapolation of efficacy is permissible from the adult efficacy studies for both products, gathering pharmacodynamic and safety data only may be sufficient.

According to NKF guidelines, the calcium-based phosphate binders in general have been shown to be safe and effective in patients with chronic kidney disease.^{8,9} There is no mention of age limitations in the guidelines. Calcium carbonate and calcium acetate are the most widely used phosphate binders, but their administration results in hypercalcemia in up to 50% of patients especially when co-administered with Vitamin D analogues.⁷ One small randomized clinical trial showed that calcium acetate has approximately three times greater phosphate binding capacity than calcium carbonate.¹⁰ As a result, theoretically, smaller doses of calcium acetate may result in similar levels of phosphate binding relative to the calcium carbonate compounds. However, in clinical practice, calcium acetate tolerability is less and patients may experience gastrointestinal irritability secondary to the acetate salt.

Recommendations to the Division for Responding to the Sponsor's Meeting Questions :

PMHS recommendations for proposed preliminary responses to the sponsor's questions in the meeting background package are below. The sponsor's original questions are provided in *italics*, followed by PMHS recommended responses in bold. Note: The following responses were generated and sent to DCaRP prior to any internal meetings on August 28, 2013. PMHS actively participated in internal discussions with the Division regarding this consult in other internal meetings held during the review of NDA 205109. Additional details, discussions, and final responses may be found in the Division's final meeting minutes for this meeting and the approval letter for NDA 205109.

Question 1: Does the Agency concur with the use and choice of the active comparator in the proposed study?

FDA Response to Question 1:

Although there are no phosphate binders approved for pediatric use in the United States, calcium-based phosphate binders are recommended in current NKF KDOQI clinical practice guidelines as first line therapy in addition to dietary restrictions. Based on your proposed safety monitoring procedures, dose adjustment, and stopping criteria, using Phoslyra (calcium-acetate) as the active comparator in this study is acceptable. However, as there is no established safety profile of Phoslyra in the pediatric population, you will need to document withdrawals, serious adverse events, and severe adverse events related to hypercalcemia and those adverse events that were commonly associated with calcium acetate in the adult study population. We recommend that if hypercalcemia develops in the control arm this should be counted as an adverse event and patients should either be withdrawn from the study, have the dose of the calcium based phosphate binder lowered, or be switched to a non-calcium containing phosphate binder. You should conduct a safety analysis of these events to determine if they occur more often in the Phoslyra group relative to the other control arm.

We note that, adequately powered, this study would provide information sufficient to label Phoslyra for use in the pediatric population as well.

Question 2: [REDACTED] (b) (4)

FDA Response to Question 2:

[REDACTED] (b) (4)

[REDACTED]

Question 3: [REDACTED] (b) (4)

[REDACTED]

FDA Response to Question 3:

(b) (4)

APPEARS THIS WAY ON ORIGINAL

Question 4: Does the Agency concur that the study design as outlined in the synopsis is sufficient to support a pediatric indication for PA21? VFMCRP seeks Agency's concurrence on the following:

- a) Selection criteria, especially with the age-related serum phosphorus levels for inclusion in the study;*
- b) Primary efficacy end-points and primary efficacy analysis for PA21;*
- c) Sample size and duration of exposure;*
- d) Age groups and age-related dosing of study medications;*
- e) Age-related target serum phosphorus levels;*
- f) Safety monitoring procedures and safety endpoint;*
- g) Palatability and acceptability patient reported outcomes (PRO) assessments*

FDA Response to Question 4:

It is premature to answer this question in totality.

(b) (4)

The study design is acceptable. The selection criteria, primary efficacy end-points, primary efficacy analysis for PA21, age-related target serum phosphorus levels, and safety monitoring procedures seem reasonable.

We have the following comments on your protocol:

- Please provide additional rationale for your starting dose and how adult clinical data were used to determine the starting dose. In the absence of PK/PD data in pediatric patients, we recommend a staged approach in which dosing is initiated in an older age cohort, with sequential enrollment of younger age cohorts if data from older age cohort(s) suggest that efficacy can be achieved and there is no emergence of a safety signal.**
- The small number of patients enrolled in the <1 year old age group are not adequate to provide meaningful safety or efficacy data. Therefore, we recommend that the proportion of patients in each of the four age groups be more similar. If you are unable to enroll a larger number of patients, you may have to provide additional support to justify partial extrapolation of your efficacy results from older pediatric patients to the younger age group.**
- In order to account for any confounding that may result from dietary restrictions, all patients should have a food diary and dietary phosphorus restriction monitored.**

PMHS Conclusions

The sponsor has submitted a synopsis of their pediatric development plan for PA21, an oral phosphate binder that will be used in patients with chronic kidney disease:

- The sponsor is proposing to conduct a single, Phase 3 pediatric clinical study, study PA-CL-PED-01, to evaluate the efficacy and safety of PA 21 in maintaining serum phosphorus**

lowering effect in pediatric patients with chronic kidney disease. Pediatric patients 28 days to 18 years will be eligible for inclusion.

- The sponsor proposed to use Phoslyra as an active comparator in the proposed pediatric plan. The sponsor of PA 21 also holds marketing rights for Phoslyra. According to the current prescribing information for Phoslyra, safety and effectiveness in pediatric patients have not been established. There is an outstanding post-marketing commitment for use of Phoslyra in pediatric patients that is scheduled for completion by March 31, 2014.
- The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) provides pediatric clinical practice guidelines for all stages of chronic kidney disease and related complications. According to NKF guidelines, the calcium-based phosphate binders in general have been shown to be safe and effective. Calcium carbonate and calcium acetate are the most widely used, but their administration results in hypercalcemia in up to 50% of patients especially when co-administered with vitamin D analogues.
- Although there are no phosphate binders approved for pediatric use in the United States, calcium-based phosphate binders are recommended in current NKF KDOQI clinical practice guidelines as first line therapy in addition to dietary restrictions. Based on the proposed safety monitoring procedures, dose adjustment, and stopping criteria, using Phoslyra (calcium-acetate) as the active comparator in this study is acceptable. However, as there is no established safety profile of Phoslyra in the pediatric population, the sponsor will need to document withdrawals, serious adverse events, and severe adverse events related to hypercalcemia and those adverse events that were commonly associated with calcium acetate in the adult study population. The sponsor should conduct a safety analysis of these events to determine if the adverse events occur more often in the Phoslyra group relative to the other control arms. Adequately powered, this study may provide information sufficient to label Phoslyra for use in the pediatric population as well.
- KDOQI clinical practice guidelines suggest that target serum phosphorus levels be maintained at or above the age-appropriate lower limits and no higher than the age-appropriate upper limits. For children with kidney failure (CKD Stage 5), including those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5-5.5 mg/dL (1.13-1.78 mmol/L) during adolescence and between 4-6 mg/dL for children between the ages of 1-12 years. Therefore a pre-defined responder analysis would be most appropriate to demonstrate a clinically meaningful response to therapy. PMHS defers to the division ultimately regarding the acceptability of the primary efficacy endpoint.
- The study design is generally acceptable. The selection criteria, age-related target serum phosphorus levels, and safety monitoring procedures seem reasonable. SEALD input is required in reference to the PRO assessments. The Division should agree with the final protocol before the sponsor proceeds with studies.
- The sponsor should provide additional rationale for the proposed starting dose including any adult clinical data that were used to determine the starting dose. In the absence of PK/PD data in pediatric patients, we recommend a staged approach in which dosing is initiated in an older age cohort, with sequential enrollment of younger age cohorts if data from older age cohort(s) suggest that efficacy can be achieved and there is no emergence of a safety signal.
- In order to account for any confounding that may result from dietary restrictions, all patients should have a food diary and dietary phosphorus restriction monitored.

PMHS Addendum:

On September 3, 2013, the sponsor submitted an amendment to the meeting package which contained a revised pediatric study protocol. The sponsor requested the Division's acceptance and comments of the proposed study changes in lieu of a face-to face meeting. The revised protocol proposed to remove Stage 1a (the fixed dose stage). Subjects would initiate study drug treatment in Stage 1 - a titration stage (formerly Stage 1b). Doses of study drug may be increased or decreased as required for efficacy. Once a study participant achieves the age specific target serum phosphorus level, then the subject enters into Stage 2.

PMHS offered the following comments to the Division on September 16, 2013, for the revised protocol. An advice letter was issued to sponsor by the Division reflecting some of PMHS concerns:

1) Elimination of Stage 1a: *PMHS defers the decision regarding the elimination of Stage 1a of the trial to DCRP in consultation with clinical pharmacology. PMHS' major concern is the selection of the appropriate dose(s) to be studied in Stage 1b of the trial, especially for patients who have not previously been treated with a phosphate binder. If necessary, the Division may also consider consulting the pediatric clinical pharmacology team.*

2) Concern for carry-over effect from previous phosphate binder usage: *The sponsor should specify a minimum number of weeks of treatment at a stable dose of phosphate binder in addition to 2 consecutive steady measurements of serum phosphorus prior to advancing to Stage 2 of the study to avoid any carry-over effect of a previous dosage level of phosphate binder.*

Appendix A Phosphorus-Binding Compounds

Compound	Common Product Names	Estimate of % Calcium Absorbed	Phosphorus (mg) Bound per mg Ca ⁺⁺ Absorbed	Estimate of Potential Binding Power	Advantages	Potential Side-effects/ Disadvantages	Possible Indications for Use
Calcium Carbonate	TUMS, Oscal, Calcichew, Caltrate, Calci-Mix, Titalac, Chooz Gum	Approximately 20%-30% is absorbed ¹⁷³	Approximately 1 mg P bound per 8 mg Ca abs (Adapted from ¹⁷³)	Approximately 39 mg P bound per 1 g Calcium Carbonate	Inexpensive, wide variety of products/availability	Hypercalcemia, extraskeletal calcification, GI side-effects, constipation	Serum parameters within target ranges to minimize risk for extraskeletal calcification
Calcium Acetate	PhosLo	With meals: 21 ±1% Between meals: 40 ±4% ¹⁷⁰	Approximately 1.04 mg P bound per mg Ca abs ¹⁷⁴ 1 mg P bound per 2.9 mg Ca abs (Adapted from ¹⁷³)	Approximately 45 mg P bound per 1 g Calcium Acetate	Less calcium absorption than CaCO ₃ ; P binding similar to Al(OH) ₃ ¹⁷⁴	Hypercalcemia, extraskeletal calcification, GI side-effects	Same as above
Calcium Citrate	Citracal	22% ¹⁷⁴	NA	NA	NA	Increases aluminum absorption	Not recommended
Compound	Common Product Names	Estimate of % Calcium Absorbed	Phosphorus (mg) Bound per mg Ca ⁺⁺ Absorbed	Estimate of Potential Binding Power	Advantages	Potential Side-effects/ Disadvantages	Possible Indications for Use
Magnesium Carbonate/ CaCO ₃	MagneBind 200/300	Has 450/300 mg calcium acetate	Approximately 1 mg P bound per 2.3 mg Ca absorbed	NA	Potential to minimize calcium load	Hypermagnesemia, no long term studies of efficacy and safety	Need to monitor serum magnesium
Aluminum Hydroxide	AlternaGEL, Alu-Cap, Aju-Tab, Amphojel, Dialume	None	NA	Liquid: Mean binding 22.3 mg P per 5 mL; Tablet/capsule mean binding 15.3 mg P per pill ¹⁷²	Effective phosphate binding	Constipation/fecal impaction, bone mineral defects, aluminum toxicity, chalky taste, GI distress, N/V	Time- and dose-limited use for hyperphosphatemia that is unresponsive to other binders
Aluminum Carbonate	Basaljel	None	NA	Same as above	Same as above	Same as above	Same as above
Sevelamer HCl	Renagel	None	NA	unknown ¹⁷⁵	Noncalcium, nonaluminum	GI side-effects, cost	Eliminates binder-related calcium load; especially appropriate for patients with hypercalcemia or extraskeletal calcification

Source: Table 9 K/DOQI Workgroup. "K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease." American Journal of Kidney Diseases. 2005.46(4):S1-S123.

Appendix B

<u>Name of Drug/NDA# (Year Approved)</u>	<u>Adult Indication</u>	<u>PREA PMR</u>	<u>Written Request Issued</u>	<u>Other Pediatric and/or Safety Comments</u>
Calcium acetate				
Phoslyra/022581 (04/18/2011)	To reduce serum phosphorus in patients with end stage renal disease	PREA-Exempt because of orphan status – (Sponsor committed to safety PMR: multiphase, placebo-controlled, dose-response phase followed by an open-label titration and maintenance phase, followed by a placebo-controlled randomized withdrawal phase)	No	Drug-drug interactions; Hypercalcemia
PhosLo/019976 and 021160 (12/10/1990)	The control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.	Plan requested in approval letter of gelpcaps	No – Inadequate PPSR	
Lanthanum carbonate				
Lanthanum carbonate/021468 (10/26/2004)	To reduce serum phosphate in patients with end stage renal disease (ESRD)	Full Waiver of PREA required studies for safety		Nonclinical studies showed deposition of drug product into bones, heart, and muscle. Long-term toxicity concerns
Sevelamer				
Renagel/020926 and 021179 (10/30/1998)	Control of serum phosphorus in patients with chronic kidney disease (CKD) who are on dialysis	(Unclear) ** Language in the original approval letter 07/12/00 "...you submitted a pediatric drug development plan. We are	Yes (1/15/02) ages 6-18yrs	Calcium acetate comparator in the WR. Sponsor declined to do studies. **Appears that sponsor was released from a pediatric

<u>Name of Drug/NDA# (Year Approved)</u>	<u>Adult Indication</u>	<u>PREA PMR</u>	<u>Written Request Issued</u>	<u>Other Pediatric and/or Safety Comments</u>
		deferring any decision on your pediatric drug development requirements until March 31, 2001."		commitment on 12/09/03
Renvela/022127 and 022318 (10/19/2007)	Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis	PREA trials originally deferred until 2009 in ages <1 month to 16 years of age. (22127) PREA trials originally deferred until 2011 in ages 0 to 18.	Yes (01/16/09) but declined by the sponsor	A noncompliance letter for failure to submit PREA-required trials was sent to sponsor on 04/11/13

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- ¹⁰ Sheikh, MS et. al. "Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical in vitro and in vivo study." *Journal of Clinical Investigations*. 1989. 83:66-73.

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/s/

ERICA WYNN
10/30/2013

HARI C SACHS
11/01/2013
I agree with the recommendations.

LYNNE P YAO
11/02/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 10, 2013

TO: Anna Park, R.Ph.,
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

FROM: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205109

APPLICANT: Vifor Fresenius Medical Care Renal Pharma France (VFMCRP)

DRUG: Velphoro (PA21) (b) (4) tab, 500 mg

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: The control of serum phosphorus levels (hyperphosphatemia) in patients with end stage renal disease (ESRD)

CONSULTATION REQUEST DATE: March 19, 2013

INSPECTION SUMMARY GOAL DATE: September 23, 2013

DIVISION ACTION GOAL DATE: November 30, 2013

PDUFA DATE: November 30, 2013

I. BACKGROUND:

Vifor Fresenius Medical Care Renal Pharma France (VFMCRP) submitted an original New Drug Application, under section 505(b)(1) of the FD&C Act for PA21 [REDACTED] (b) (4) [REDACTED] chewable tablet, 500 mg for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD). The application is based on the results of an open-label, randomized, active-controlled, parallel group, multicenter, phase 3 study to investigate the safety and efficacy of PA21 compared with sevelamer carbonate followed by a randomized comparison of PA21 maintenance dose versus PA21 low dose (LD) in dialysis patients with hyperphosphataemia (Protocol Number PA-CL-05A) and is supported by several additional studies. Current marketed products, including sevelamer, the comparator used in this study, are effective in reducing serum phosphorus levels, but have a high pill burden, decreasing compliance.

PA21 is an oral iron containing phosphate binder that is being developed by Vifor Pharma for therapeutic use in the control of hyperphosphatemia in adult patients with CKD on dialysis. The product, PA21, is a mixture of polynuclear iron (III)-oxyhydroxide, starch and sucrose with an optimized affinity to phosphate at a pH of 3 to 8. Following oral administration, PA21 reportedly adsorbs the dietary phosphate in the gastrointestinal tract, preventing its uptake into the blood, thereby reducing the serum level of phosphate.

Protocol Number PA-CL-05A: An Open-label, Randomized, Active-controlled, Parallel Group, Multicenter, Phase 3 Study to Investigate the Safety and Efficacy of PA21 Compared with Sevelamer Carbonate Followed by a Randomized Comparison of PA21 Maintenance Dose Versus PA21 Low Dose (LD) in Dialysis Patients with Hyperphosphataemia.

The study population included males and females of any race/ethnicity, who were 18 years of age and older, and who were receiving maintenance HD or PD. This trial was performed at 174 centers in 15 countries noted below:

- 66 centers screened patients and 65 centers randomized subjects in the USA, (n=516)
- 56 centers screened patients and 49 centers randomized subjects in Europe: Austria, Belgium, Czech Republic, Germany, Latvia, Lithuania, Poland, Romania, United Kingdom, (n=236)
- 52 centers screened patients and 47 centers randomized subjects in the rest of the world (Croatia, Russia, Serbia, South Africa, Ukraine), (n=307).

The primary endpoint analysis of the study was comparison between the maintenance dose and the low dose group in the change in serum phosphorus levels from Week 24 to Week 27 in the primary efficacy set of subjects on hemodialysis. The safety variables in this study included

adverse events profile and routine biochemical/hematological laboratory tests (including liver function tests). Sites were chosen on the basis of high enrollment and a high number of treatment responders.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Susan Adele Diamond, M.D. Site 833	PA-CL-05A / n=22	July 1-5, 2013	Pending (preliminary NAI)
Kaldun Nossuli, M.D. Site 841	PA-CL-05A / n=15	June 3-7, 2013	Pending (preliminary NAI)
Robert Hootkins, M.D. Site 832	PA-CL-05A / n=21	April 22-26, 2013	Pending (preliminary VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Susan Adele Diamond, M.D.**

San Antonio Kidney Disease Center
Physicians Group PLLC
8042 Wurzbach Road, Suite 500
San Antonio, TX 78229

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811. There were 15 INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection. This inspection was performed as a data audit for Protocol PA-CL-05A.

There were a total of 31 subjects screened, and 22 of these were enrolled into the study. A total of 20 subjects completed the study (2 subjects withdrew early). An in depth audit of the study records for 23 subjects (14 randomized subjects and 9 screen failures) was conducted.

b. General observations/commentary:

There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were eight SAEs recorded at this site and no deaths. No evidence of underreporting of AEs or SAEs was observed. No significant deficiencies were found and a Form FDA 483 was not issued. Two discussion items were discussed with the Clinical Investigator regarding the inadequacy of dispensing of investigational product to 11 subjects, and laboratory specimens not collected for 6 subjects at Visit 5 and Visit 7. Both were reportedly attributed to misinterpretation of the protocol by study staff. The two discussion items did not affect the safety of the study subjects because their phosphate levels were closely monitored, and the subjects never ran out of product.

c. Assessment of data integrity:

Data from this study site appear reliable and can be used in support of the indication.

2. Kaldun Nossuli, M.D., P.A.

6420 Rockledge Drive
Suite 1100
Bethesda, MD 20814

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811. There was one IND associated with the inspected entity in CDER's database, and the CI had no prior inspection. This inspection was performed as a data audit for Protocol PA-CL-05A.

There were a total of 26 subjects screened, and 15 of these were enrolled into the study. A total of 13 subjects completed the study and 2 subjects discontinued from the study. The two subjects were Subject # 909 who received transplant at week 12 and Subject # 924 who developed an adverse event of rash at week 8. An in depth audit of the study records for 6 subjects was conducted.

b. General observations/commentary:

There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were no SAEs recorded at this site. No significant deficiencies were observed and a Form FDA 483 was not issued. In general, the study was conducted appropriately.

c. Assessment of data integrity:

No regulatory violations were noted and a Form FDA 483 Inspectional Observations was not issued. Data from this study site appear reliable.

3. Robert Hootkins, M.D.

Research Management, Inc.
12221 N. Mopac Expressway
Austin, TX 78758

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811. There were 10 INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection.

This inspection was performed as a data audit for Protocol PA-CL-05A. There were a total of 32 subjects screened, and 21 subjects were enrolled into the study. The following 5 subjects discontinued the study: Subject #s 901/(b) (6) (patient relocation), 909/(b) (6) (PI discretion on patient noncompliance), 919/(b) (6) (recurrent constipation and abdominal cramping), 927/(b) (6) (intracranial hemorrhage/SAE), and 931/(b) (6) (nausea and emesis). A total of 15 subjects completed the study. An in depth audit of the study records for 21 subjects was conducted.

b. General observations/commentary:

There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were eight subjects who had SAEs recorded at this site and the SAEs were reported to the sponsor. A Form FDA 483, Inspectional Observations, was issued to this investigator for the following:

1. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,

Protocol exclusion criterion # 12 states that subjects with hypocalcaemia (total serum calcium < 7.6 mg/dL) at screening should be excluded from the study. Subjects who do meet the protocol exclusion criteria were enrolled into the study without notifying the sponsor. Subject # 909/(b) (6) was enrolled into the study even though the patient's serum calcium values were 6.7, 6.2, 7.4, and 7.0 mg/dL at screening Visit 1, washout period Visit 2, washout period Visit 3 and washout period Visit 3, respectively. In addition, protocol exclusion criterion #1 states that subjects with intact parathyroid hormone (iPTH) levels >800 ng/L at screening should be excluded from the study. Subject # 915/(b) (6) had an iPTH value of 1282.7 pg/mL at screening and the patient was enrolled into the study.

OSI Reviewer Comments: The clinical investigator should have excluded the above two subjects from participation in this study based on the above exclusion criterion. The clinical investigator's written response to the 483 dated June 26, 2013 acknowledged this protocol deviation. He stated that he had implemented corrective actions to study site SOPs to prevent similar recurrences.

Because the findings appear isolated, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site,

- a) Per protocol, dose modifications based on the target serum phosphate level range of 2.5 to 5.5 mg/dL were not properly done for eight subjects at various time points during Week 2 to Week 24 :

Subject	Week	Serum Phos level (mg/dl)	(g/day)
901/ (b) (6)	2	6.3	5
	6	5.9	5
904/ (b) (6)	8	5.7	4.8
	12	8.2	7.5
907/ (b) (6)	16	8.8	7.5
	20	6.6	7.5
908/ (b) (6)	20	6.8	7.5
	4	6.5	7.2
911/ (b) (6)	6	6.6	9.6
	8	6.7	9.6
915/ (b) (6)	8	7.8	7.5
	8	6.4	4.8
918/ (b) (6)	16	6.3	4.8
921/ (b) (6)	6	5.7	9.6

OSI Reviewer Comments: *The clinical investigator should have performed protocol required dose adjustments based on the target serum phosphate level according to the investigational plan. Dr. Hootkins provided a written response to the Form FDA 483 dated June 26, 2013.*

According to the CI, reasons as to why dosage was not adjusted were linked to either to subject's compliance or diet. In addition, several dose adjustments were made the week following the actual visit when the lab was drawn. The CI stated that the delay in dose adjustment was due to the delay in receiving blood values from the central laboratory.

- b) The protocol states “The occurrence of an SAE must be immediately reported to the sponsor or its delegate within 24 hours of awareness by facsimile, email or telephone.” For the subjects in the table below, the SAEs were not reported within 24 hours.

Subject	Date Of Initial SAE Report	Date of Sig of Reporter	Deviation
901/ (b) (6)	11/21/2011	11/21/2011	SAE (Death), Faxed to sponsor > 24 hrs
903/ (b) (6)	3/12/2011	3/15/2011	SAE (Stroke) Faxed to sponsor > 24 hrs
910/ (b) (6)	5/9/2011	5/9/2011	SAE (Surgery for Wrist Fracture) Faxed to sponsor > 24 hrs
913/ (b) (6)	5/11/2011	5/11/2011	SAE (Gangrene, toe amputation) , Faxed to sponsor > 24 hrs
918/ (b) (6)	11/23/2011	11/23/2011	SAE, Infected peritoneal catheter (peritonitis), Faxed to sponsor > 24 hrs
926/ (b) (6)	1/19/2012	1/19/2012	SAE (chest pain, non-cardiac), Faxed to sponsor > 24 hrs
931/ (b) (6)	11/7/2011	11/7/2011	SAE (hemorrhage from fistula site), Faxed to sponsor > 24 hrs
931/ (b) (6)	10/5/2011	10/6/2011	SAE (hemorrhage from fistula site), Faxed to sponsor > 24 hrs

OSI Reviewer Comments: *Written response (dated June 26, 2013) to the Form FDA 483 by the CI acknowledged these protocol deviations. The protocol deviations described above are noted in the data listings submitted by the sponsor. The CI stated that he had implemented corrective actions.*

- c) Facility Signatures on Delegation of Authority Log requires completion and documentation of staff training for the protocol prior to commencing the study procedures. The in service trainings for dialysis facility staff as well as the clinic manager of the dialysis unit were not properly documented.

OSI Reviewer Comments: *According to Dr. Robert Hootkins’ written response (dated June 26, 2013) to the Form FDA 483 that contains supporting documents, protocol specific training sessions for the FMC dialysis staff were held on December 30, 2010 and August 5, 2011. At the 30DEC2010 training session, the dialysis staff and the clinic*

manager did sign the Delegation of Authority log at the required training. Sign in sheets were not used for this training, only the Delegation of Authority log. A sign-in sheet was not used for the training that was done on August 5, 2011.

The clinical investigator failed to appropriately document the in service training for dialysis facility staff and the clinic manager. The clinical investigator should have appropriately documented the in-service training. Although, the CI failed to appropriately document the required in-service training for dialysis facility staff and the clinic manager, it appears that they were trained to perform protocol specified work. The failure not to use sign-in sheet was reportedly an administrative error. The observed violations do not appear to significantly affect data reliability, nor do they compromise the rights, safety and welfare of subjects in the study.

- d) The protocol states "Blood pressure and HR will be measured with the subject in a sitting position after 5 minutes of rest for Visit 6, 8, 10, 12, 13, 14, 15, and 16." Vital signs (BP and HR) were not obtained following a 5 minutes sitting rest in seven subjects: Subject 912/ (b) (6) (Visits 14 and 15), Subject 920/ (b) (6) (Visits 13, 14, 15, 16), Subject 921/ (b) (6) (Visit 16), Subject 926/ (b) (6) (Visits 4, 10, 15), Subject 927/ (b) (6) (Visits 1, 2, 3, 10), Subject 929/ (b) (6) (Visits 4, 10, 12, 13), Subject 931/ (b) (6) (Visits 2, 3, 6). Vital signs were not obtained before dialysis was initiated in 3 subjects: Subject 901/ (b) (6) (Visit 6), Subject 909/ (b) (6) (Visit 3) Subject 929/ (b) (6) (Visit 16).

OSI Reviewer Comments: *According to the clinical investigator written response (dated June 26, 2013) to the Form FDA 483 which contains copies of source documents, vital signs were obtained in all the subjects. The root cause of the observation identified above was caused by incorrect documentation of the times vital signs were performed.*

Although the clinical investigator failed to ensure proper documentation of the times vital signs were captured, the violation unlikely affect subject safety or data reliability.

- e) The protocol states ".. laboratory samples will be collected before dialysis is initiated ... Blood samples for ... efficacy and safety assessments ... will be drawn in accordance with the schedule of events".
- Per protocol, predialysis laboratory tests were to be performed at various visits during the study. The recorded timelines for pre dialysis laboratory sample collection were inaccurate for the

following subjects: Subject #s 907/ (b) (6) (Visits 13, 25, 16), 909/ (b) (6) (Visit 7) Subject 910/ (b) (6) (Visits 1, 7, 13), Subject 911/ (b) (6) (Visits 2, 3, 5, 6, 10, 16), Subject 912/ (b) (6) (Visits 7, 8, 13), Subject 917/ (b) (6) (Visits 2, 3, 6, 16), Subject 926/ (b) (6) (Visits 1 and 16), Subject 929/ (b) (6) (Visit 13).

OSI Reviewer Comments: According to Dr. Robert Hootkins' written response (dated June 26, 2013) to the Form FDA 483, he stated that the pre-dialysis blood tests were done prior to dialysis initiation and acknowledged the discrepancy was caused by error in transcribing the time laboratory samples were collected. For example, the observations identified above were caused due to improper documentation of the time blood samples were collected. For example: For subject # 917, written time of blood draw was recorded by dialysis staff as 5:40AM. Flow sheets show that dialysis was initiated at 5:37AM. However, blood draw times were entered from 5:31 to 5:32 AM for a variety of labs and for heparin administration which is administered post lab bloodwork collection. Also for the same subject, Visit 16 shows a blood draw collection of 6:01AM. Dialysis was initiated at 5:40AM. On the flow sheet, a hemoglobin blood draw was documented at 5:21 AM followed by heparin administration which documents blood draws were performed prior to dialysis.

Dr. Hootkins acknowledged discrepancy in documentation of the times that blood samples were collected and stated that he has implemented corrective action. The above-mentioned findings are unlikely to affect subject safety or data reliability.

- Per the protocol, pre/post dialysis BUN lab samples were required for calculating Kt/V assessment. In five patients, pre and post BUN blood samples were not collected (Subject #s 902/ (b) (6) (Visits 13 and 16), 904/ (b) (6) (Visit 8), 908/ (b) (6) (VISIT 13), 911/ (b) (6) (Visit 4), 917 / (b) (6) (Visit 19))

OSI Reviewer Comments: Dr. Robert Hootkins written response to the Form FDA 483 acknowledged this protocol deviation. OSI reviewer recommends that the review division determines the potential impact, if any, that not having pre and post dialysis BUN labs that are required to calculate Kt/V assessments.

c. Assessment of data integrity:

Although regulatory violations were noted above, it is unlikely, based on the isolated nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site. OSI recommends that the review division determine the potential impact, if any, that not having pre and post dialysis BUN labs that are required to calculate Kt/V assessments.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators, Drs. Kaldun Nossuli, Susan Adele Diamond and Robert Hootkins, were inspected for this application. The preliminary classification for the inspections of Drs. Kaldun Nossuli and Susan Adele Diamond inspections is No Action Indicated (NAI). The classification for Dr. Robert Hootkins is Voluntary Action Indicated (VAI). For this site, OSI recommends that the review division determine the potential impact, if any, that not having pre and post dialysis BUN labs that are required to calculate Kt/V assessments. Except for this issue, the data derived from all inspected sites are considered reliable in support of the application.

Note: Observations noted above are based on the Form FDA 483, communications with the field investigator and preliminary review of the establishment inspection reports (EIRs); an inspection summary addendum will entered into DARRTS if conclusions change upon final review of the EIRs.

{See appended electronic signature page}

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/s/

KASSA AYALEW
10/11/2013

SUSAN LEIBENHAUT
10/11/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 5, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Velphoro (Sucroferric Oxyhydroxide) Chewable Tablet, 500 mg

Application Type/Number: NDA 205109

Applicant/Sponsor: Vifor Inc.

OSE RCM #: 2013-684

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

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1 INTRODUCTION

This review evaluates the proposed labels and labeling for Velphoro (b) (4) for areas of vulnerability that can lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the May 30, 2013 labeling submission.

- Active Ingredient: Sucroferric Oxyhydroxide
- Indication of Use: Control of serum phosphorus levels in patients with end-stage renal disease (ESRD)
- Route of Administration: Oral
- Dosage Form: Chewable Tablet
- Strength: 500 mg
- Dose and Frequency: The recommended starting dose is 1500 mg (3 tablets) per day, administered as 1 tablet (500 mg) 3 times daily with meals. Serum phosphorus levels should be monitored and the dose titrated in decrements or increments of 500 mg (1 tablet) per day as needed until acceptable serum phosphorus level (less or equal to 5.5 mg/dL) is reached, with regular monitoring afterwards. Titration can be started as early as 1 week after treatment initiation. Based on clinical studies, on average patients required 3 to 4 tablets (1,500 mg to 2,000 mg) a day to control serum phosphorus levels. The highest daily dose studied in a Phase 3 clinical trial in ESRD patients was 6 tablets (3,000 mg) per day.
- How Supplied: Brown, circular, bi-planar, chewable tablets embossed with “PA 500” on one side. Each tablet contains 500 mg iron as (b) (4) and will be packaged in bottles of 30 tablets or 90 tablets (b) (4)
- Storage: Store at 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Store in the original package and keep the bottle tightly closed in order to protect from moisture. The shelf life is 18 months.
- Container and Closure Systems: There are 2 container closure systems for the drug product. The bottle configuration consists of a high density polypropylene bottles (HDPE) bottle (b) (4) The blister configuration consists of (b) (4) The bottles or blister units are contained inside a paperboard carton.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted September 19, 2013 (no image)
- Container Label for 30-count (physician samples) and 90-count bottles submitted on September 19, 2013 (Appendix A)
-  (b) (4)
- Carton Labeling for 30-count (physician samples) and 90-count bottles submitted on September 19, 2013 (Appendix C)
-  (b) (4)

3 MEDICATION ERROR RISK ASSESSMENT

We were initially concerned about the clinical impact if the tablet is not fully chewed before swallowing (i.e. risk of impaction in the gut, choking, etc.). However, further discussions with ONDQA and the Medical Officer indicate there is no evidence to suggest that there will be any impaction in the gut and the tablets should dissolve fully if swallowed by accident.

Our review of the proposed container label, blister label, and carton labeling identified areas of vulnerability. These include the following:

- Overly prominent graphic near the proprietary name
- Inadequate prominence of the statement of strength due to location and size
- Lack of important information such as chewing tablets and not swallowing whole
- Net quantity placed too close to the statement of strength
- Inadequate prominence of established name
- Use of dangerous symbols in the insert labeling

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved for clarity and to increase the readability and prominence of important information on the label to promote the safe use of the product.

DMEPA advises the following recommendations be implemented prior to approval of this NDA. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. We recommend revising the Dosage and Administration section (Section 2) under *Starting Dose* to read "...1 tablet (500 mg) by mouth 3 times daily with meals (1500 mg per day)."
2. Because the symbol ' \leq ' appears on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations, we recommend using the terms "less than or equal to" instead of the symbol in the Dosage and Administration section (Section 2) to avoid being mistaken as the opposite of its intended meaning.

4.2 COMMENTS TO THE APPLICANT

A. General comments on all container labels and carton labeling

1. Revise the presentation of the proprietary name from all caps (i.e. VELPHORO) to title case (i.e. Velphoro) to improve readability of the name.
2. The proposed proprietary name "VELPHORO" is printed in two colors ("PHO" is blue in color and "VEL---RO" is black). This can be considered to be analogous to the use of tall-man lettering which is typically reserved for differentiating known look-alike and sound-alike established name pairs or in rare circumstances for proprietary names to help reduce the risk of wrong drug name errors.² Since Velphoro is not a name that has been involved in drug name confusion or wrong drug errors, the use of different font colors in the name is inappropriately applied. Revise the proprietary name presentation so it is presented in a single font type and color.
3. Remove or minimize and move away the graphic near the proprietary name since it is distracting, competes with the prominence of the name, and may be mistaken as the letter 'O'.
4. Ensure that the established name (including the dosage formulation) is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2). The entire established name, including the active ingredient and the dosage form, should be presented in the same font.
5. Relocate the strength statement to appear below the established name statement on the principal display panel (PDP).
6. Debold the "Rx Only" statement and ensure the font size is smaller than the proprietary name, established name, and strength to minimize its prominence.

² Michael R. Cohen, Medication Errors, 2nd ed., American Pharmacists Association, Washington, D.C., 2007, pp. 89-90.

B. Blister Label

1. Remove the 'Rx only' statement to reduce clutter on the small label.
2. Debold and condense the distributor information to create more white space on this small label and improve readability.
3. The light grey color used for the NDC number is difficult to read. We recommend using a font color that will improve readability.

C. Container Label and Carton Labeling (30-count physician samples)

1. Increase the prominence of the statement "Physician Sample – Not For Sale" to avoid overlooking this important information.

D. Carton Labeling (30-count physician samples and 90-count bottles)

1. The back panel looks too similar to the principal display panel (PDP), which can lead to the wrong panel being displayed on a shelf during stocking. Revise the back panel to ensure adequate differentiation from the PDP.
2. Remove the proprietary name and established name printed vertically since it is not easily readable without having to turn or rotate the container and is redundant. Ensure the presentation of the proprietary name and established name on the principal display panel is prominently displayed, horizontally, in a manner congruent with the container labels.
3. Add the statement "Tablet must be chewed" on the principal display panel.
4. Relocate the net quantity statement from the back panel to the PDP. Ensure it is located away from the statement of strength.

E. Carton Labeling (b) (4)

1. (b) (4)
2. (b) (4)

F. Carton Labeling (b) (4)

1. (b) (4)

G. Bottle Container Label

1. Delete the words (b) (4) from the "Tablets must be chewed..." statement and increase the prominence of the "Tablets must be chewed" statement.
2. Delete the (b) (4) statement since it clutters the label and is not required.
3. The label is currently cluttered making it difficult to read the information being presented. Additionally, a reader will be required to turn the bottle to read the most important information. Therefore, we recommend rearranging the label into two sections: a principal display panel (PDP) and a side panel. The proprietary name,

established name, strength, net quantity, and chewing warning should be retained on the PDP. Ensure the net quantity statement is located on the bottom of the PDP away from the strength statement while the “salt equivalent” statement is relocated to the side panel.

4. Delete the statement [REDACTED] (b) (4) [REDACTED] as it is repetitive and clutters the PDP. The asterisk may be relocated to follow the strength statement on the PDP.

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

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

/s/

KIMBERLY A DE FRONZO
10/05/2013

IRENE Z CHAN
10/05/2013

RHPM NDA Overview
20 November 2013

NDA 205109

Sponsor: Fresenius Medical Care North America
Classification: 5/S

Indication: control of serum phosphorus levels in patients with chronic kidney disease on dialysis

Date of Application: February 1, 2013

Goal Date: December 1, 2013

Background:

Velphoro (b) (4) PA21) is an iron-based phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. The proposed dose of Velphoro is 3 tablets (1500 mg) per day administered as 1 tablet (500 mg) 3 times daily with meals.

The applicant's clinical development program includes two studies, Study PA-CL-05A and Study PA-CL-03A that provides the main support for efficacy. Study PA-CL-05A, the pivotal phase 3 trial, was a 27-week, 2-stage re-randomization, withdrawal study with a 24-week randomized, open-label, active-controlled first stage in which PA21 was compared to both baseline and sevelamer carbonate for lowering serum phosphorus in ESRD patients on HD or PD. Study PA-CL-03A was a phase 2, 6-week open-label, randomized, active-controlled, dose-ranging study (250 to 2500 mg/day PA21) in ESRD patients on HD. Study PA-CL-05B was a 28-week extension study to Study PA-CL-05A and mainly examined the safety and tolerability of PA21 compared to sevelamer carbonate in patients on either HD or PD. However, data from this study were also used to evaluate long-term efficacy (changes from baseline to 12 months in serum phosphorus levels on PA21 compared to sevelamer). An additional study, PA1201, conducted in Japanese patients, also provides some efficacy data.

Reviews: *(Please note these are summaries and not complete reviews. Please refer to their complete reviews in DARRTS).*

Division Director's Memo (November 27, 2013)

Reviewer: Norman Stockbridge, M.D., Ph.D.

Conclusion: Approval

Summary: Please refer to his review in DARRTS.

CDTL (November 8, 2013)

Reviewer: Shen Xiao, M.D.

Conclusion: Approval

Labeling:

The proposed proprietary name Velphoro (b) (4) has been reviewed by the Division of Medication Error Prevention and Analysis and is found acceptable from both a promotional and safety perspective. The previous proposed proprietary name, (b) (4) was found unacceptable (b) (4)

A draft labeling containing the Division's recommendations has been shared with the Applicant. As noted in sections 7 and 13, revisions are needed to the text describing drug-drug interactions and non-clinical toxicology findings; some other changes in wording and corrections have also been made. Agreement needs to be reached prior to approval.

Summary:

Recommend that Velphoro (PA21) be approved for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on hemodialysis (HD) or peritoneal dialysis (PD) therapy.

Risk Benefit Assessment

The efficacy of Velphoro for the control of serum phosphorus level in ESRD patients on dialysis was demonstrated in a pivotal study and a dose-ranging study. The development program also provides evidence of the product's long-term effectiveness in controlling serum phosphorus levels.

As with other non-absorbed medicines, safety findings were primarily limited to GI adverse events. Diarrhea was the most common adverse event on Velphoro. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued use of Velphoro. No new or significant safety signals have emerged with long-term treatment in the safety extension study, and the findings from this study suggest maintenance of efficacy with chronic administration and a favorable tolerability profile. No safety concerns were raised by a comprehensive assessment of laboratory tests which included hematology and chemistry tests and ECGs. No significant iron accumulation was observed during treatment for up to 52 weeks in a long term study. The effects of Velphoro™ on the bioavailability of other drugs commonly used in ESRD patients have also been sufficiently characterized (b) (4)

Overall, Velphoro has a favorable benefit/risk profile as a treatment for the control of serum phosphorus levels in patients with ESRD.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

Based on the information available in the current submission, I do not have any recommendations for post market risk evaluation and mitigation strategies.

Recommendation for other Postmarketing Requirements and Commitments

Pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) should be conducted but will be deferred until after approval. The applicant has submitted their pediatric plan

(b) (4)

(b) (4)

Medical (July 7, 2013)

Reviewer: Shen Xiao, M.D.

Conclusion: Approval

Labeling: None at this time

Summary:

Velphoro™ demonstrated clinically and statistically significant reductions in serum phosphorus levels at therapeutic doses compared to a non-effective low dose control in one pivotal study. Velphoro™ was also effective in lowering phosphorus levels in a dose ranging, active-controlled trial. Collectively, the pivotal study, its one year extension study, and the dose-ranging study provide evidence that Velphoro™ is effective in lowering serum phosphorus levels and that efficacy is maintained during chronic administration. In these trials, Velphoro's™ effect on serum phosphorus was also similar to that observed with the active control, sevelamer (37% and 40% reduction from baseline in the Velphoro™ and Sevelamer treatment arms, respectively, in the pivotal phase 3 trial).

As with other phosphate binders, adverse reactions were primarily limited to the GI tract. Diarrhea was the most common adverse event (AE) in the Velphoro™ treatment arm and was reported at a higher incidence on Velphoro™. Diarrhea was also the major reason for AE-related patient withdrawal on Velphoro™. The majority of these diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. The incidence of other common GI AEs, including nausea, vomiting and constipation, appeared to be lower in the Velphoro™ arm when compared to the active control. The incidence of these common GI events was substantially lower during continued treatment in the study extension. No new or significant safety signals were observed during long-term treatment of up to one year.

Because Velphoro™ is an iron-based phosphate binder, effects on iron-related parameters were studied. Though increases in serum ferritin and TSAT were observed during the first 6 months of treatment with Velphoro™, further increases were not observed with continued treatment up to one year. There was also no evidence of iron accumulation with increased cumulative exposure. The concomitant use of IV iron and ESAs in these studies and regional differences in their use should be considered when

interpreting these findings. Nonetheless, the results are consistent with a Phase 1 clinical pharmacology study which demonstrated minimal iron absorption.

Several drug-drug interaction studies (both in vitro and in vivo) were conducted to investigate Velphoro's™ effect on the bioavailability of other drugs. In in vivo studies conducted in healthy subjects, concomitant administration of Velphoro™ did not affect the bioavailability (based on measured AUC) of drugs commonly used in ESRD patients including losartan, furosemide, digoxin, warfarin, and omeprazole. In in vitro drug-drug interaction studies, there was no effect of Velphoro™ on ciprofloxacin, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, and quinidine. However, Velphoro™ did affect alendronate, doxycycline, levothyroxine, atorvastatin, and paricalcitol. The applicant's proposed labeling recommends

(b) (4)

(b) (4)

(u) (u) In the pivotal study, Velphoro™ did not appear to affect the lipid lowering effects of HMG-CoA reductase inhibitors.

Overall, the AE profile of Velphoro™ is considered to be acceptable for a product used to control serum phosphorus levels in patients with end stage renal disease who are being treated with hemodialysis or peritoneal dialysis. Velphoro™ may also have a lower pill burden compared to some other phosphate binders. In the clinical studies, the average patient required 3 to 4 tablets a day.

Statistical (September 21, 2013)

Reviewer: Ququan (Cherry) Liu, Ph.D.

Conclusion: Approval

Labeling: None

Summary:

An active comparator of sevelamer was used in both studies

(b) (4)

(b) (4) . Therefore the result of non-inferiority in the submission was not evaluated (b) (4)

Some issues were identified for Study 3a:

- The majority was non-US patients and the US population was under-represented.
- The result of Study 3a may be questionable for the following identified issues:
 - After final CSR has completed, some issues were discovered including inconsistencies between the original datasets and the final CSR, problems related to the programming and algorithm derivations.

- Some post hoc manipulations were made including revising SAP, re-conducting analyses and updating CSR.

Two clinical studies (3a & 5a) were submitted to support the efficacy of PA21 in control of serum phosphorus levels in patients with end-stage renal disease (ESRD). Study 5a appears to demonstrate that PA21 maintenance dose (1000-3000 mg/day) is superior to the low dose (1.25 mg/day). Though a dose-response effect is suggested from Study 3a, the result of the study may be questionable due to post hoc manipulations of data.

Pharmacology (April 25 and October 8, 2013)

Reviewer: Baichun Yang, Ph.D.

Conclusion: Approval

Labeling: Please refer to her April 25, 2013 review in DARRTS.

Summary Please refer to her reviews in DARRTS.

Clinical Pharmacology Review (July 2, 2013)

Reviewer: Ju-Ping Lai, Ph.D.

Conclusion: Approval

Labeling: Please refer to her review in DARRTS.

Summary:

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical pharmacology information submitted in the NDA 205-109. The submission is acceptable from a clinical pharmacology perspective provided an agreement is reached on the Agency's proposed labeling recommendations.

Biopharmaceutics Review (March 25, 2013 and November 7, 2013)

Reviewer: Elsbeth Chikhale, Ph.D.

Conclusion: Approval

Labeling: None

Summary:

The following dissolution method and acceptance criterion are acceptable for batch release and stability testing. From a Biopharmaceutics perspective, NDA 205109 for Velphoro (sucroferric oxyhydroxide) Chewable Tablets is recommended for APPROVAL.

Product Quality (September 27 and November 11, 2013)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 205109	NDA Supplement #:S- BLA Supplement #
Efficacy Supplement Type SE-	
Proprietary Name: Velphoro	
Established/Proper Name: PA21 (b) (4)	
Dosage Form: Chewable tablet	
Strengths: 500mg	
Applicant: Vifor Fresenius Medical Care Renal Pharma	
Agent for Applicant (if applicable): Fresenius Medical Care North America	
Date of Application: January 30, 2013	
Date of Receipt: February 1, 2013	
Date clock started after UN:	
PDUFA Goal Date: December 1, 2013	Action Goal Date (if different): November 30, 2013
Filing Date: April 2, 2013	Date of Filing Meeting: February 14, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only): Type 1	
Proposed indication(s)/Proposed change(s): Control of serum phosphorus levels in patients with end stage renal disease (ESRD).	
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>	
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 75610				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			PeRC Meeting scheduled for October 2, 2013
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): March 31, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 19, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): February 21, 2008	X			Carcinogenicity
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 14, 2013

BLA/NDA/Supp #: NDA 2105109

PROPRIETARY NAME: Velphoro

ESTABLISHED/PROPER NAME: PA21 (b) (4)

DOSAGE FORM/STRENGTH: Chewable Tablet, 500 mg

APPLICANT: Vifor Fresenius Medical Care Renal Pharma

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): oral phosphate binder for the control of serum phosphorus levels in patients with end stage renal disease (ESRD).

BACKGROUND: Vifor Fresenius Medical Care Renal Pharma submitted a 505(b)(1) NDA for PA21 (b) (4) a new oral iron-based phosphate binder, for the control of serum phosphorus levels in patients with end stage renal disease (ESRD).

Each tablet contains 500 mg iron as (b) (4) The proposed starting dose is 1,500 mg/day (3 tablets/day) with meals; the dose should be adjusted, to optimize serum phosphorus levels (≤ 5.5 mg/dL), by a single tablet per day. The dose may be decreased or increased by 500 mg (1 tablet) per day every 2 to 4 weeks, to a minimum of 1,000 mg/day and a maximum of 3,000 mg/day based on serum phosphorus level

Summary of Key Regulatory Milestones:

August 18, 2006	IND for PA21 (b) (4) submitted
October 6, 2006	Pre-IND Meeting
January 15, 2008	Carcinogenicity Special Protocol Assessment (SPA) submitted
February 21, 2008	Carcinogenicity SPA Agreement granted
March 31, 2010	End-of-Phase 2 Meeting
August 13, 2010	Meeting request submitted to discuss their Pediatric Development Plan, deferral and a waiver in a subset of the population. Office of Pediatrics and Maternal Health Staff (PMHS) was consulted and agreed with the deferral. Meeting was canceled on October 26, 2010 as the preliminary responses (sent November 22, 2010) explained the necessary steps for a pediatric plan.
September 19, 2012	Pre-NDA Meeting
November 7, 2012	Discussion of Topline results

The sponsor's clinical program includes:

- Two Phase 1 studies: Q-24120 and VIT-CI-01/02;
- Five drug-drug interactions studies;
- Two pivotal studies: PA-CL-03A (Phase 2) and PA-CL-05A (Phase 3); and

- A long-term safety extension study PA-CL-05B. Results will be available in the second quarter of 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anna Park	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shen Xiao		Y
Clinical	Reviewer:	Shen Xiao	Y
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ju-Ping Lai	Y
	TL:	Rajnikanth Madabushi	Y
Biostatistics	Reviewer:	Ququan (Cherry) Liu	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Baichun Yang	Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Thomas Wong	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Thomas Wong	Y
	TL:	Kasturi Srinivasachar	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kim DeFronzo	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers (Biopharmaceutics)	Elsbeth Chikhale		Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Please provide study report and datasets for the Japanese study (PA1201) to allow adequate Dose-Response relationship analysis.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Please provide statistical analysis programs for the analyses of primary and secondary endpoints.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>BIOPHARMACEUTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Will need to confirm PA21 is not an NME</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge, M.D., Ph.D.	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): **July 2, 2013**

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none">• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)• notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ANNA J PARK
04/16/2013