

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205109Orig1s000

CHEMISTRY REVIEW(S)

NDA 205-109

**VelphoroTM (Suroferric oxyhydroxide) 500 mg
Chewable Tablet)**

Vifor Fresenius Medical Care Renal Pharma

Thomas M. Wong, Ph.D.

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature: See DARRTS	8
B. Endorsement Block: See DARRTS	8
C. CC Block See DARRTS.....	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE.....	9
P DRUG PRODUCT	54
A APPENDICES	109
R REGIONAL INFORMATION	109
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	110
A. Labeling & Package Insert	110
B. Environmental Assessment Or Claim Of Categorical Exclusion	115
III. List Of Deficiencies To Be Communicated:.....	115

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA: 205-109
2. REVIEW #: 1
3. REVIEW DATE: September 27, 2013
4. REVIEWER: Thomas M Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 75,610	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	Feb 1, 2013
Amendment # 0003	Feb 19, 2013
Amendment # 0008	Mar 29, 2013
Amendment # 0011	Apr 19, 2013
Amendment # 0012	Apr 29, 2013
Amendment # 0020	Aug 9, 2013
Amendment # 0023	Aug 22, 2013
Amendment # 0025	Aug 29, 2013
Amendment # 0027	Sep 19, 2013
Amendment # 0028	Sep 24, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Vifor Fresenius Medical Care Renal Pharma France

Address: 12, Rue de la Chaussee d'Antin
Paris, France, 75009

Fresenius Medical Care North America

U.S. Representative: Michael Bauer, Ph.D., Director, Global Regulatory Affairs
Ruth Turner, Director, Regulatory Affairs Pharmaceuticals

Telephone: 781-699-4654

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Velphoro
b) Non-Proprietary Name (USAN): Sucroferric oxyhydroxide
c) Code Name/# (ONDC only): PA21
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Control of serum phosphate levels in patients with end stage renal disease (ESRD)

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 500 mg iron (III)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

USAN: Sucroferric oxyhydroxide

Chemistry Review Data Sheet

CAS Name: Mixture of iron(III)-oxyhydroxide, sucrose, Starches
 Polynuclear iron(III)-oxyhydroxide stabilized with sucrose, and starches

CAS registry number:

β-iron(III)-oxyhydroxide: CAS No. 12134-57-5

Sucrose: CAS No. 57-50-1

Starch: CAS No. 9005-25-8

(b) (4)

Molecular formula: $pn\text{-FeOOH} + x\text{C}_{12}\text{H}_{22}\text{O}_{11} + y(\text{C}_6\text{H}_{10}\text{O}_5)_n$

Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	4			Sufficient information in application
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 75,610	Commercial IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Apr 3, 2013	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	N/A		
DMFPA	N/A		
EA	Acceptable	Sep 27, 2013	Thomas Wong
Microbiology	N/A		

Executive Summary Section

The Chemistry Review for NDA 205-109

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 205-109 for Velphoro™ (sucroferic oxyhydroxide) chewable tablet, 500 mg, cannot be approved from the CMC perspective due to the following pending issue.

Acceptance of dissolution specification has not been resolved between the biopharmaceutics reviewer and the applicant.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Drug product

The applicant has developed a chewable tablet for (b) (4) oral administration for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. The trade name for sucroferic oxyhydroxide chewable tablet is Velphoro™ and the tablets are red-brown, round, flat-faced chewable tablet embossed with “PA 500” and is approximately (b) (4). Each tablet contains 500 mg elemental iron equivalent to 2500 mg sucroferic oxyhydroxide complex and the following excipients: woodberry flavor, neohesperidin dihydrochalcone, magnesium stearate, and silica. The tablets will be manufactured by Vifor SA in Switzerland and by (b) (4) in Germany. Commercial batch size for the Vifor and (b) (4) facility is (b) (4) tablets and (b) (4) tablets, respectively. Tablets are packaged in HDPE bottles with 30 counts and 90 counts per bottle. (b) (4)

Tablets are stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). Available 18 months stability data supports 30-month expiration dating period for the tablets when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

Drug substance

Sucroferic oxyhydroxide is a complex which consists of the polynuclear iron (III)-oxyhydroxide, sucrose and starch. The pn-FeOOH moiety is produced as an aqueous suspension, it is chemically not stable and cannot be isolated and stored as an active pharmaceutical ingredient. (b) (4)

(b) (4) Polynuclear iron (III)-oxyhydroxide is a phosphate binder and exhibits minimal release of iron across the range of pH values found in the GI tract. It adsorbs the dietary phosphate in the GI tract, preventing its

Executive Summary Section

uptake into the blood, and thereby reducing the serum level of phosphorus. The phosphate bound to polynuclear iron (III)-oxyhydroxide is subsequently eliminated in the feces. The polynuclear iron (III)-oxyhydroxide is prepared by (b) (4)

(b) (4)
The drug (b) (4) substance is manufactured in Vifor (International) Inc., in Switzerland. (b) (4) a commercial batch size for PA21 ranging between (b) (4) is proposed. The applicant provided adequate information regarding structure elucidation. Available 48 months stability data at both 25°C/60% RH and 30°C/75% RH storage conditions supports a (b) (4) re-test dating when stored at 30°C/65% RH and packaged into (b) (4)

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

The recommended starting dose of Velphoro is 3 tablets (1,500 mg iron) per day, administered as 1 tablet (500 mg iron) 3 times daily with meals. Tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, tablets may be crushed.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. NDA 205-109 for Velphoro™ (sucroferric oxyhydroxide) 500 mg Chewable Tablet cannot be approved as per CMC perspective due to pending issue mentioned in Section 1A above.

III. Administrative

- A. **Reviewer's Signature:** See DARRTS
- B. **Endorsement Block:** See DARRTS
- C. **CC Block** See DARRTS

109 Pages 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/

THOMAS M WONG
09/27/2013

RAMESH K SOOD
09/27/2013

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 205109
Applicant: Vifor Fresenius Medical Care Renal Pharma
Letter Date: Jan 30, 2013
Stamp Date: Feb 1, 2013
PDUFA Date: Dec 1, 2013 (Standard Review)
Tradename: To be submitted
Established Name: [REDACTED] (b) (4)
Dosage Form: Chewable Tablets, 500 mg Fe (III)
Route of Administration: Oral
Indication: Control of serum phosphate levels in patients with end stage renal disease (ESRD)
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Figure 1 Schematic Diagram of the Structure of PA21

Summary

This is an e-CTD 505(b)(1) NDA for a new phosphate binder with the code name PA21 which consists of polynuclear iron (III) oxyhydroxide stabilized with sucrose and mixed with starches (b)(4). This is formulated into chewable tablets each containing 500 mg iron. The drug is indicated for the control of serum phosphorus levels in patients with end-stage renal disease. Upon oral administration with a meal, phosphate binding takes place in the GI tract by ligand exchange between the hydroxyl groups and/or water and the phosphate ions. Iron is minimally absorbed since the polynuclear iron oxyhydroxide is insoluble.

PA21 was developed under IND 75,610 and is intended to be a safe and effective calcium, aluminum and lanthanum free phosphate binder, with a reduced pill burden compared to other approved products for this indication.

There was only one meeting with the firm where CMC topics were discussed, a pre-NDA CMC meeting held on Dec. 7, 2012. The issues covered included the definition of the drug substance, the need for (b)(4) as part of the drug substance specification, (b)(4)

(b)(4)
There was considerable discussion on the definition of the drug substance. (b)(4)

(b)(4)
Agreement was reached that (b)(4)

(b)(4)
Vifor was also told that the Agency did not agree to (b)(4)
(b)(4)

Drug Substance

The Applicant refers to the mixture of polynuclear iron (III) oxyhydroxide (pn-FeOOH) sucrose and starches as the drug substance (PA21). (b)(4)

(b)(4)
The manufacturing process for PA21 consists of (b)(4)

(b) (4)
It is stated that the quality of the drug substance is not influenced by the scale of manufacture and a commercial batch size of (b) (4) is proposed. (b) (4)

Specifications are proposed for the drug substance which include the usual test attributes, appearance, identification, LOD, and assay (iron, sucrose and starch) and microbiological quality. In addition, there are tests for particle size, sodium content and in-vitro phosphate adsorption. Batch analysis results for non-clinical, clinical, stability and process validation batches, ranging in size from (b) (4) have been provided. Both packaging configurations have been used in the stability studies of PA21. Three batches, all over (b) (4) manufactured in June 2010, and stored at 30°C/75%RH, 25°C/60%RH and 40°C/75% RH have been studied and 12 -18 months long term data are available. 48 months' data from two earlier, smaller scale (b) (4) batches packaged in (b) (4) are also reported. The stability protocol includes tests for assay (iron, starch, sucrose), iron release, in vitro phosphate adsorption, LOD and particle size. Forced degradation studies have also been conducted. A retest period of (b) (4) is proposed for the drug substance stored at or below 30°C and packaged in (b) (4)

Drug Product

PA21 chewable tablets are manufactured in only one strength which is equivalent to 500 mg of iron. The tablets are red brown, round, flat faced and approximately 20 mm in diameter and 6 mm in thickness, with a nominal mass of (b) (4). The excipients used are magnesium stearate and colloidal silicon dioxide which are compendial as well as Woodberry flavor and the (b) (4) neohesperidine dihydrochalcone. Woodberry flavor is not in USP or Ph. Eur. but is stated to comply with the European Council Regulation No. 1334/2008 on flavorings. Reference to (b) (4) is provided. Neohesperidine dihydrochalcone is also not in USP but has a Ph. Eur monograph.

There are two primary drug product manufacturing sites, one at Vifor in Switzerland and the other at (b) (4) in Germany. The same manufacturing process is used at both sites but the nominal batch sizes are (b) (4)

The manufacturing process consists of (b) (4). The formulation and manufacturing process has evolved from material used for Phase I and 2 trials to the current Phase 3 and proposed commercial process. (b) (4)

The manufacturing process development contains some elements of QbD starting with the identification of the QTPP, the related CQAs and risk assessment of the ability of the process to reliably produce product of the intended quality. The functional relationships that link material attributes and process parameters to the CQAs were determined by DoE studies with 2 production scale batches and 20 sub-batches. The tableting speed, main compression force and

drug substance lot were identified as critical input parameters. A design space was defined for the tableting speed – (b) (4) a range which was claimed to be confirmed by DOE. The main compression force is the key parameter for setting up the tableting equipment and must be adjusted based on the physical binding properties of the drug substance lot used for the drug product manufacture. The compression force correlates with tablets hardness and will be set (b) (4)

PA21 tablets are packaged in HDPE bottles (b) (4)

The specification proposed for the product includes standard test attributes like ID, assay, LOD, uniformity of dosage units and microbiological quality. In addition, attributes like tablet hardness and disintegration time which are critical for a chewable tablet have been proposed as well as unique critical tests for this drug such as in vitro phosphate adsorption and iron release. There is no impurity specification since it is claimed that there is no impurity in the product which is not present in the drug substance. Batch analysis data have been provided for numerous batches used in the clinical trials as well as commercial scale validation batches manufactured at both Swiss and German sites.

Stability data have been submitted from both manufacturing sites. The batch sizes for the 3 batches each from Vifor, Switzerland and (b) (4) Germany are (b) (4) tablets and (b) (4) tablets respectively. Six months' long term data from the Swiss site and 9 months' long term data from the German site are available for product packaged in bottles (b) (4) 6 months' data under accelerated storage conditions have been submitted for both sites. Based on the results from these studies an initial shelf-life of (b) (4) is proposed. In-use stability studies have been carried out on 90 count bottles (b) (4)

It is claimed that the test results at the end of (b) (4) support a (b) (4) Other special stability studies performed include bulk tablet storage stability and photostability.

Critical Review Issues

Drug Substance

- Is the active moiety ferric ion or polynuclear ferric oxyhydroxide?
- The firm had been told earlier that polynuclear ferric oxyhydroxide is not an NME, however recently they have sent in a rebuttal. Does this change our original decision?
- Has the proposed structure of pn-FeOOH been adequately characterized?
- Is the structure of akaganeite (β -FeOOH) well established in the literature? How is it prepared? This is important since it is stated that the XANES spectrum of PA21 batches shows good correlation with the reference spectrum of akaganeite.
- Is the manufacturing process of PA21 described in adequate detail?
- Are the specifications for metallic impurities in the raw material, (b) (4) acceptable? Has a rationale been provided for the selection of metal impurities to be included? Are the proposed acceptance criteria satisfactory? This should be discussed with the pharm/tox reviewer -- they had concerns about (b) (4) levels during development.
- Are the proposals for skip testing of the components, (b) (4) acceptable?

- The firm was advised in the pre-NDA meeting to clarify how they monitor reaction completion in the (b) (4) step. (b) (4)
- Regarding the specification:
 - The Applicant has not yet included the (b) (4) test and states that they are working on it. This should be in place with test results for some batches for completion of the CMC review.
 - For many tests, the Applicant has proposed 2 analytical methods e.g. complexometric titration or NIRS for assay of iron, spectrophotometry or ICP-OES for in-vitro phosphate adsorption. For some of these tests they designate one method as the reference method which is presumably the regulatory method. However, they have a footnote to the specification table stating that the reference method is performed at least once a year. Is it clear that the alternate method is performed on every batch at release? Have they demonstrated the equivalency of both methods?
 - It is not clear what the applicant means in footnote 6 (b) (4) for microbiological tests.
 - Are the acceptance criteria for particle size and in-vitro phosphate adsorption adequately justified?
 - The table should be reformatted removing many of the footnotes. References for tests such as microbiological quality should be to USP <61> and <62> (b) (4)
 - It is stated that the iron release test, which was historically included in the stability protocol, will not be part of future stability studies since it is not stability indicating. Is this acceptable? Should this test be done for batch release?
- Is the proposed retest date of (b) (4) for the drug substance acceptable?

Drug Product

- Biopharm has indicated that a dissolution test is needed for this product. A method development report has been submitted. Acceptance of the method and limits is the responsibility of the Biopharm reviewer.
- Excipient compatibility with the drug substance should be evaluated. (b) (4)
- (b) (4)
- How much information has been provided for the (b) (4) neohesperidin dihydrochalcone, since this ingredient doesn't seem to have been used in US approved drugs?
- The manufacturing process development report should be reviewed in-depth including the DoEs performed.
- Are the in-process parameters and acceptance criteria for (b) (4) the manufacturing process satisfactory?
- Tableting speed, main compression force and drug substance lot have been identified as critical input parameters and based on DoE and validation studies it is stated that a design

space has been created for these parameters. Is this a bona fide design space or are these merely the validated ranges for the tableting equipment?

- Has the design space been incorporated into the manufacturing process description (MBR)?
- Regarding the specification:
 - Many of the issues identified with the drug substance specification are also present here – too many footnotes, references to Ph. Eur. when relevant USP methods exist for common attributes such as uniformity of dosage units, microbiological quality etc.
 - Two methods are specified for some tests like ID and in-vitro phosphate adsorption without delineating one as the regulatory and the other as the alternative procedure.
 - The two methods for identification, a color reaction/precipitation of iron versus NIR cannot be considered equivalent since the former only establishes the presence of iron whereas the latter should be specific for the mixture of polynuclear ferric oxyhydroxide, sucrose and starches. The Applicant should be recommended to use both methods for identification.
 - (b) (4) testing is proposed for microbiological quality.
 - The hardness limits are quite broad considering that this is a critical attribute for chewable tablets. Are different release and shelf-life ranges acceptable?
 - Dissolution testing has not been included in the specification
 - The iron release test is for shelf-life only and will not be performed at release. Is there justification for this?
- The DMF (b) (4)
- A (b) (4) is proposed based on the additional stability data provided in a recent amendment. Is this acceptable? An acceptance criterion for iron release has not been established and is needed before an expiration dating period is granted. If dissolution testing is required, how is the absence of stability data for this parameter going to be handled?
- Should the annual stability commitment include (b) (4) from each of the sites?

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES and the overall recommendation is currently "Pending"; the reviewer should confirm the completeness and accuracy of the entries. A categorical exclusion from environmental assessment has been requested. Methods validation will be not be initiated at this time since this not an NME. However, the reviewer should evaluate the non-traditional methods used for the drug substance and drug product to see if methods validation is called for. A single CMC reviewer is recommended since the drug product is a traditional chewable tablet composed of

(b) (4)

Kasturi Srinivasachar
CMC Lead

Mar. 12, 2013
Date

Ramesh Sood
Branch Chief

Mar. 12, 2013
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 205109
NDA Type: 3
Original NDA, N-000

Established/Proper Name:



Applicant: Vifor Fresenius Medical Care Renal Pharma france
Letter Date: Jan 30 , 2013
Stamp Date: Feb 1, 2013

PDUFA Goal: Dec 1, 2013 (Standard Review)

CMC Reviewer: Thomas Wong

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
-----	---	---	--	--

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Some QbD elements provided
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LoAs to DMFs for [REDACTED] (b) (4) provided

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharm Section
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharm filing review
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			

FDA ORDER LES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 205109/000
 Reg. Code: 110
 Priority: 5
 Receipt Date: 01-FEB-2013
 DUFA Date: 01-DEC-2013
 Submission Goal:
 District Goal: 02-OCT-2013

Sponsor: VIFOR FRESENIUS
 920 WINTER ST
 WALTHAM, MA 02451
 Brand Name: FERRIC OXYHYDROXIDE SUCROSTAMIX
 Estab. Name:
 Generic Name: FERRIC OXYHYDROXIDE SUCROSTAMIX
 Product Number; Dosage Form; Ingredient; Strengths
 001; TABLET; INGREDIENT TERM PENDING; 500MG

DA Contacts:	T. WONG	Prod Qual Reviewer	(HFD-810)	3017961608
	D. MESMER	Product Quality PM	(HFD-800)	3017964023
	A. PARK	Regulatory Project Mgr		3017961129
	K. SRINIVASACHAR	Team Leader		3017961760

Overall Recommendation: ACCEPTABLE on 03-APR-2013 by J. WILLIAMS () 3017964196
 PENDING on 15-FEB-2013 by EES_PROD

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

MF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 04-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA ORDER 110
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9613378 FEI: 3002808450
VIFOR INTERNATIONAL INC.
RESCHENSTRASSE 37
ST. GALLEN, , SWITZERLAND CH-9001

MF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 19-FEB-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: (b) (4) API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 19-FEB-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: FEI: 3009018997
VIFOR PHARMA
RTE DE MONCOR 10
VILLARS-SUR-GLANE, FR, SWITZERLAND

MF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 03-APR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

KASTURI SRINIVASACHAR
03/12/2013

RAMESH K SOOD
03/12/2013