

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203565Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 203565/000
Org. Code: 161
Priority: 5
Stamp Date: 03-OCT-2011
PDUFA Date: 30-JUL-2013
Action Goal:
District Goal: 31-MAY-2013

Sponsor: LUITPOLD PHARMS
 800 ADAMS AVE STE 100
 NORRISTOWN, PA 19403
Brand Name: Injectafer
Estab. Name: Ferric Carboxymaltose
Generic Name:
Product Number; Dosage Form; Ingredient; Strengths
 001; INJECTION; FERRIC CARBOXYMALTOSE; 50MG

FDA Contacts:	S. LIN	Prod Qual Reviewer		3017961403
	S. LANGILLE	Micro Reviewer	(HFD-805)	3017961557
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	A. BAIRD	Regulatory Project Mgr		3017964969
	J. BROWN	Team Leader		3017961652

Overall Recommendation:	ACCEPTABLE	on	(b) (4)	by J. WILLIAMS	()	3017964196
	PENDING	on	(b) (4)	by EES_PROD		
	ACCEPTABLE	on	(b) (4)	by J. WILLIAMS	()	3017964196
	PENDING	on	(b) (4)	by EES_PROD		
	WITHHOLD	on	(b) (4)	by D. SMITH	(HFD-620)	2402769592

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-MAY-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-APR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-FEB-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-JUN-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

MEMORANDUM

DATE July 8, 2013
FROM William M. Adams, CMC Reviewer
TO NDA 203565
SUBJECT Final OC recommendation for NDA 203565 in EES

NDA 203565 for Injectafer® (ferric carboxymaltose injection) re-submitted on 30 Jan 2013 with manufacture and control sites that differ from those listed in the initial NDA submission. CMC Review #3 (dated 25-Jun-2013) concluded that the application should not be approved in that an overall acceptable recommendation from the Office of Compliance and labeling issues were pending.

The Office of Compliance issued an overall recommendation of Acceptable on 05-Jul-2013 and labeling meetings have been scheduled. Accordingly, from a CMC perspective, NDA 203565 is considered to be acceptable for approval.

William M. Adams
CMC Reviewer, Branch II/DNDQA I/ONDQA

Ali al Hakim, Ph.D.
Chief, Branch II/DNDQA I/ONDQA

cc:
DHP/RPM/A.Baird
DNDQA I/PMQ/J.Martin
DNDQA I/CMC Lead/J.Brown

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/s/

WILLIAM M ADAMS
07/19/2013

ALI H AL HAKIM
07/21/2013

NDA 203,565

**Injectafer® (Ferric Carboxymaltose Injection)
50 mg Iron/mL**

Luitpold Pharmaceuticals, Inc.

William M. Adams

**Division of New Drug Quality Assessment I/Branch II
Office of New Drug Quality Assessment**

**For the Division of Hematology Products
Office of Hematology and Oncology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. **NDA 203,565**
2. **REVIEW 03**
3. **REVIEW DATE:** 25 Jun 2013
4. **REVIEWER:** William Adams
5. **PREVIOUS DOCUMENTS:**

S-000	Original submission	09 Sep 2011
S-004	Response to FDA filing issues	06 Jan 2012
S-006	Photostability study	08-Feb-2012
S-007	Response to 03/19/12 Micro IR letter	26 Mar 2012
S-008	Response to 03/26/12 CMC IR letter	13 Apr 2012
S-009	Response to FDA request	23 Apr 2012
S-010	Response to FDA request for NDA section 3.2.S.4.4	24 Apr 2012
S-011	Up-dated in-use stability data	27 Apr 2012
S-012	Revised heavy metal limits	16 May 2012
S-013	Response to 05/30/12 CMC IR letter	06/ Jn 2012
	CMC Review 01	08 Jun 2012
	CMC Review 02 (EES conclusion)	09 Jul 2012
	Complete Response	23 Jul 2012

6. SUBMISSION(S) BEING REVIEWED:

S-015	Response to IR – labeling comments	18 Jul 2012
S-016	Type B meeting request	13 Sep 2012
S-017	Meeting package	29 Oct 2012
S-018	Stability summary	06 Dec 2012
S-019	Resubmission, class 2	30 Jan 2013
S-020	DP manufacturing site address	05 Feb 2013
S-023	Proprietary name proposal	02 Apr 2013
S-024	Response to 04/02/13 Micro IR letter	12 Apr 2013
S-025	Updated DP stability data	06 May 2013
S-026	Response to 05/25/13 CMC IR letter	31 May 2013
S-027	Response to 06/12/13 CMC IR letter	13 Jun 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Luitpold Pharmaceuticals, Inc.
 Address: PO Box 9001, One Luitpold Drive
 Shirley, NY 11967

CMC Review Data Sheet

Representative: Marsha E. Simon
 800 Adams Avenue, Suite 100
 Norristown, PA 19403
 Telephone: 610-650-4200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Injectafer®
- b) Non-Proprietary Name (USAN): Ferric Carboxymaltose Injection
- c) Code Name/# (ONDQA only): VIT-45
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chemical Type: 2
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of iron deficiency anemia

11. DOSAGE FORM: Injection for IV infusion

12. STRENGTH/POTENCY: 50 mg iron/mL

13. ROUTE OF ADMINISTRATION: IV infusion

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:

Molecular Formula $[\text{FeO}_x(\text{OH})_y(\text{H}_2\text{O})_z]_n \{(\text{C}_6\text{H}_{10}\text{O}_5)_m(\text{C}_6\text{H}_{12}\text{O}_7)_1\}_k$ where $n \sim 1000$, $m \sim 8$, $l \sim 11$, $k \sim 4$
 Molecular Weight ~150,000 daltons
 Molecular Structure see CMC Review 01

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF#	Type	Holder	Item Referenced	Code ¹	Status ²	Review Date	Comments ³
16967	II	Vifor International	drug substance (VIT-45 powder)	4	active		
(b) (4)	III	(b) (4)	(b) (4)	4	active		

CMC Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	4	active		
	III			4	active		
	III			4	closed 04/15/11		
	III			4	active		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Document	Owner	Item Referenced	Status	Review Date	Comments
IND 63,243	Luitpold Pharmaceuticals (Norristown, PA)	VIT-45 Injection/ Injectafer®	Active as of 05/06/06		
NDA 22,054	Luitpold Pharmaceuticals (Norristown, PA)	Injectafer®	Not approved as of 03/11/08		

18. CONSULTS/CMC-RELATED REVIEWS:

Consults	Subject	Date Forwarded	Reviewer	Status
EES	GMP for CMC sites	04/17/12	OC	Pending OC overall conclusion
Biopharm	biowaiver	---	M.Hughes	not needed
DMEPA	proposed trade name	02/23/12	K.DeFranco	accepted
Methods Validation	none	---	---	package sent to (b) (4) for NDA 22,054, thus not for this NDA
PharmTox	residual metal limits		B.Gehrke	accepted
Microbiology	sterility assurance		S.Donald	accepted

Executive Summary Section

The CMC Review for NDA 203,565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Complete and acceptable chemistry, manufacturing, and controls (CMC) information has been provided to support approval of this application, however an overall recommendation by the Office of Compliance (OC) for the GMP inspections of the proposed manufacturing and testing facilities for the drug substance and drug product is still *pending*. Therefore, the application cannot be approved.

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product when stored at the USP controlled room temperature.

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

None

II. Summary of CMC Assessments

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

DRUG SUBSTANCE

Ferric carboxymaltose is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*- α -*D*-glucopyranosyl)-oxy-2R,3S,5R,6-tetrahydroxy-hexanoate with a relative molecular weight of approximately 150,000 daltons. Bulk drug is a brown amorphous powder readily soluble in water, but insoluble in most organic solvents (e.g., (b) (4)).

Complete and acceptable CMC information is provided in type II drug master file (DMF) 16967, owned by Vifor International, Inc., and summarized in the application. A letter of authorization for the DMF has been provided. DMF 16967 was reviewed on 07-Jun-2012 and found to be adequate to support this application. No significant changes have been made to the DMF since that review. Vifor is responsible for drug substance manufacture and all testing except residual solvents testing which is performed by a contract laboratory.

The proposed drug substance is a new complex of iron rather than a new molecular entity (NME). Although ferric carboxymaltose has not been approved for use in a commercial drug product, the active moiety is iron (III). In addition, there are multiple FDA approved iron (III)-

Executive Summary Section

carbohydrate drug products for which iron (III) is the active moiety and drug product strength is expressed in terms of iron content (e.g., iron dextran injection and iron sucrose injection).

All CMC issues regarding drug substance were resolved in the first review cycle. The resubmission proposes no changes to the drug substance section of the NDA. The CMC information regarding drug substance is acceptable to support approval of the application, however an overall conclusion by OC for the application is still *pending*.

DRUG PRODUCT

Injectafer® (ferric carboxymaltose injection) is a dark brown, sterile, aqueous solution intended for intravenous use in the treatment of iron deficiency anemia in patients intolerant to oral iron preparations or with chronic kidney disease. The drug product is designed to release usable iron (III) to the iron transport and storage proteins in the body.

Injectafer® will be marketed as a 15 mL single-use glass vial containing 750 mg of iron, formulated as ferric carboxymaltose, at 50 mg iron/mL strength. Drug product contains ferric carboxymaltose in water for injection with no excipients except sodium hydroxide and/or hydrochloric acid which are added to adjust the pH.

The drug product is manufactured by (b) (4) processing followed by (b) (4) sterilization. The manufacturing process and controls are described in sufficient detail. No quality by design information is provided and design spaces are not proposed. The process has been reviewed and found acceptable for sterility assurance at the proposed drug product manufacturing site.

The specification for product release and stability testing is acceptable in that the tests address the appropriate attributes for identity, purity and assay; and the proposed acceptance criteria are adequately justified. The analytical methods are described in sufficient detail and have been shown to be valid for their intended use at the site of use. Acceptable reference standards have been developed for testing.

The submitted stability data is sufficient to support the proposed 24-month expiration dating period with storage at controlled room temperature.

All CMC issues were resolved in the first review cycle, however the site proposed for drug product manufacture and testing failed its cGMP inspection and a Complete Response was issued. The resubmission proposed a new site for manufacture and multiple contract laboratories for testing. Revisions to the manufacturing process and analytical methods due to the site changes were introduced. The release and stability specifications are unchanged. Complete and acceptable CMC information has been provided to support approval of the new manufacturing and testing sites. The proposed sites have been found to meet cGMP requirements, however an overall conclusion by OC for the application is still *pending*.

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

Executive Summary Section

Injectafer® is a parenteral iron replacement product indicated for the treatment of iron deficiency anemia in patients with intolerance to oral preparations or chronic kidney disease. The dosage of Injectafer® is expressed as mg of elemental iron (III).

For iron deficiency anemia, the recommended dose is 15 mg/kg body weight up to a single dose of 750 mg administered on two occasions at least 7 days apart. Drug is administered as either an undiluted slow IV push at 100 mg/minute or by drip infusion diluted in 250 mL normal saline administered over 15 minutes. For stability reasons, dilutions to concentrations less than 2 mg iron/mL are not permissible.

For hemodialysis dependent chronic kidney disease, the recommended dose is (b) (4) mg administered as undiluted IV push into the venous line of the dialyzer for (b) (4) consecutive treatment sessions

C. Basis for Approvability or Not-Approval Recommendation

The CMC information for drug substance is provided by reference to Vifor's type II DMF 16967 which has been reviewed and found adequate to support approval of this application. Complete and adequate CMC information has been provided to assure the quality and stability of the drug product.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Injectafer®.

CMC comments on the proposed vial and cartons labels and the package insert are *pending* internal FDA labeling meetings.

An overall recommendation from OC for the application is still *pending*.

III. Administrative

A. Reviewer's Signature: (See appended electronic signature page)

William M. Adams
CMC Reviewer/Branch II/DNDQA I/ONDQA

B. Endorsement Block:

Ali al Hakim, Ph.D.
Chief/Branch II/DNDQA I/ONDQA

C. CC Block: entered electronically in DFS

DHP/RPM/A.Baird
DNDQA I/PMQ/J.Martin
ONDQA I/CMC Lead/J.Brown

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/s/

WILLIAM M ADAMS
06/26/2013

ALI H AL HAKIM
06/26/2013

MEMORANDUM

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

DATE: July 9, 2012
FROM: Sue-Ching Lin, CMC Reviewer
TO: **NDA 203565**
SUBJECT: Final CMC recommendation for NDA 203565

NDA 203565 for Injectafer[®] (ferric carboxymaltose injection) was initially submitted on 30-Sep-2011 and was granted a standard review by the Agency. Chemistry Review #1 (dated 08-Jun-2012) recommended approval of NDA 203565 pending the receipt of an overall acceptable recommendation from the Office of Compliance.

This memo serves to update that determination. The Office of Compliance issued an overall withhold recommendation for this application on 05-Jul-2012. Accordingly, from a CMC perspective, approval of NDA 203565 cannot be recommended until any related deficiencies are resolved.

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/s/

SUE CHING LIN
07/09/2012

JANICE T BROWN
07/09/2012

NDA 203565

Injectafer[®]
(ferric carboxymaltose injection)

Luitpold Pharmaceuticals, Inc.

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
Review of Original NDA
For the Division of Hematology Products

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CMC Review Data Sheet

1. NDA 203565
2. REVIEW #: 1
3. REVIEW DATE: 08-Jun-2012
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 63,243 submission	15-Jan-2004
Original IND 63,243 CMC review	12-Feb-2004
NDA 22-054 original NDA submission	15-Jun-2006
NDA 22-054 CMC Review #1	15-June-2007
NDA 22-054 not-approvable letter	09-Jul-2007
NDA 22-054 resubmission	12-Sep-2007
NDA 22-054 CMC Review #2	19-Feb-2008
NDA 22-054 not-approvable letter (clinical deficiencies only)	11-Mar-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	09-Sep-2011	03-Oct-2011
Amendment (Response to FDA filing review issues)	5	06-Jan-2012	06-Jan-2012
Amendment (Photostability results)	7	08-Feb-2012	08-Feb-2012
Amendment (Response to 3/19/12 microbiology IR)	8	26-Mar-2012	26-Mar-2012
Amendment (Response to 3/26/12 CMC IR)	9	13-Apr-2012	13-Apr-2012
Amendment (Response to FDA request to change e-CTD format to provide revisions in respective module/sections)	10	23-Apr-2012	23-Apr-2012
Amendment (Response to FDA request for section 3.2.S.4.4)	11	24-Apr-2012	24-Apr-2012
Amendment (Updated in-use stability data)	12	27-Apr-2012	27-Apr-2012
Amendment (Revised heavy metal limits)	13	16-May-2012	16-May-2012
Amendment (Response to 5/30/12 CMC IR)	14	06-Jun-2012	06-Jun-2012

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Luitpold Pharmaceuticals, Inc.
Address: PO Box 9001, One Luitpold Drive
Shirley, NY 11967
Representative: Marsha E. Simon, Manager, Regulatory Affairs
800 Adams Avenue, Suite 100
Norristown, PA
Telephone: 610-650-4200 ext. 207
610-650-0114 (fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Injectafer[®]
b) Non-Proprietary Name: ferric carboxymaltose injection
c) Code Name/# (ONDQA only): VIT-45
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 2 (new complex of iron)
 - Submission Priority: standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: treatment of iron deficiency anemia

11. DOSAGE FORM: injection, solution

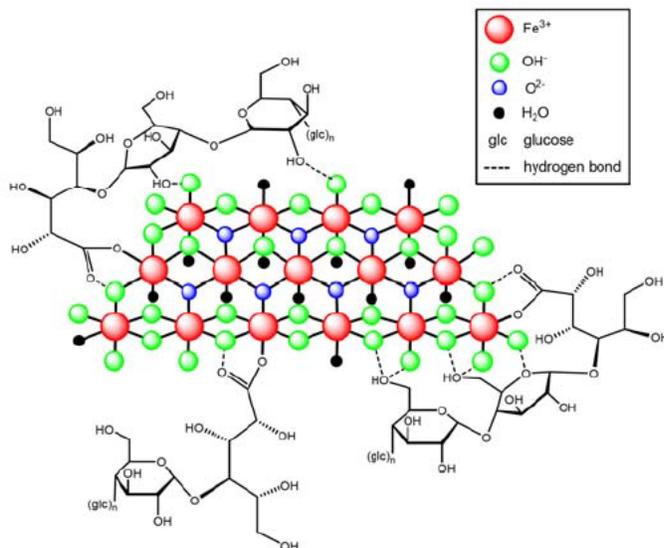
12. STRENGTH/POTENCY: 50 mg iron/mL ((b) (4)
750 mg iron /15 mL)

13. ROUTE OF ADMINISTRATION: intravenous (slow push injection or infusion)

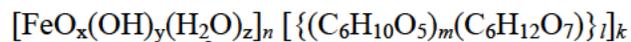
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

CMC Review Data Sheet

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



Molecular formula:



Where: $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$

(l represents the mean branching degree of the ligand)

Molecular mass: $\sim 150,000$ Daltons

USAN: ferric carboxymaltose

Chemical name: Polynuclear iron (III)-hydroxide 4(R)-(poly-(1 \rightarrow 4)-*O*- α -D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate

Company or laboratory code: VIT-45

Chemical Abstracts Service (CAS) registry number: 9007-72-1

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
16967	II	Vifor International Inc.	Drug substance: VIT-45 Powder	1	Adequate	07-Jun-2012	Reviewed by Sue-Ching Lin
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	See current review	See section 3.2.P.7
	III			4	N/A	See current review	See section 3.2.P.7

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,243	VIT-45 intravenous injection
NDA	22-054	Injectafer [®]

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending*	Pending	Pending
Pharm/Tox	The proposed acceptance criteria for (b)(4) are acceptable.	25-May-2012	Brenda Gehrke, Ph.D.
Biopharm	N/A*		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA ***	The proposed proprietary name Injectafer [®] is acceptable.	23-Feb-2012	Kimberly DeFronzo, Pharm.D.
EA	Categorical exclusion (see review)	Date of this review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint.	08-May-2012	Stephen E. Langille, Ph.D.

*The inspection of Luitpold, the drug product manufacturer, is still pending. The drug substance manufacturing and testing sites are acceptable.

**Dr. Minerva Hughes, biopharm reviewer, stated in her 10/18/11 e-mail that there are no biopharm issues and a biopharmaceutics reviewer is not need for this NDA.

***DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an “acceptable” overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product.

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product when stored at the proposed controlled room temperature.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance ferric carboxymaltose is an iron-carbohydrate complex. Specifically, it is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Daltons.

Ferric carboxymaltose is a brown amorphous powder readily soluble in water, insoluble in most organic solvents like (b) (4).

Detailed information on the drug substance is referenced to DMF 16967, held by Vifor International Inc. A letter of authorization has been provided. DMF 16967 was reviewed by this reviewer on 07-Jun-2012 and found to be adequate to support this NDA .

Although ferric carboxymaltose has not been used in approved drug products, it is not a new molecular entity (NME). A NME is a compound that contains an active moiety that has never been approved by FDA or marketed in the United States. For

Executive Summary Section

this drug substance, the active moiety is iron (III). There have been approved iron (III)-carbohydrate drug products on the market (e.g., iron dextran injection and iron sucrose injection) for which iron (III) is also the active moiety and the strengths of the products are expressed in terms of iron. Therefore, the drug substance is a new complex of iron rather than a NME.

(2) Drug Product

Injectafer[®] (ferric carboxymaltose injection) is a dark brown, sterile, aqueous solution intended for intravenous use for the treatment of iron deficiency anemia. The drug product is designed to release utilizable iron to the iron transport and storage proteins in the body.

Injectafer[®] will be supplied in (b) (4) 15 mL single use vials respectively providing (b) (4) 750 mg of iron (as ferric carboxymaltose). All vials are filled from a (b) (4) 50 mg/mL solution. The drug product contains ferric carboxymaltose in water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH.

The drug product is manufactured by (b) (4) processing followed by (b) (4) sterilization. The sterile processing has been reviewed by Dr. Stephen Langille, microbiology reviewer, and found to be adequate.

The submitted stability data support the proposed 24-month expiration dating period for the drug product stored at the proposed controlled room temperature.

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

Injectafer[®] is a parenteral iron replacement product indicated for the treatment of iron deficiency anemia. The dosage of Injectafer[®] is expressed in terms of mg of elemental iron. The recommended dosage is 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron. Evaluate the hematologic and iron indices for response (hemoglobin, ferritin, iron, and transferrin saturation) at least one month following the second Injectafer[®] administration. Injectafer[®] treatment may be repeated if iron deficiency reoccurs.

Injectafer[®] must be administered intravenously, either as an undiluted slow intravenous push or by drip infusion. When administered via slow intravenous push, up to 750 mg of iron is delivered at the rate of approximately 100 mg per minute. When administered via drip infusion, 750 mg of iron is diluted in 250 mL of sterile 0.9% sodium chloride injection, USP and administered over 15 minutes. For stability reasons, dilutions to concentrations less than 2 mg iron/ml are not permissible.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Full CMC information has been submitted to this NDA. Therefore, this review is based on the information provided in this NDA, despite the applicant's proposal to cross reference the previous CMC information in NDA 22-054 (b) (4)

The CMC information of the drug substance was referenced to DMF 16967, which has been reviewed by this reviewer and found to be adequate. This reviewer has consulted the pharm/tox team (Dr. Brenda Gehrke, pharm/tox reviewer, and Dr. Haleh Saber, pharm/tox team leader) regarding the acceptability of the proposed limits for (b) (4). The drug substance specification, as revised in the 06-Jun-2012 amendment of the NDA, is adequate.

Adequate data have been provided to ensure the quality of the drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. The revised drug product specification, as submitted in the 23-Apr-2012 amendment, is adequate.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Injectafer.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. This reviewer had shared the labeling comments regarding container labels and carton labeling with the DMEPA reviewers before the labeling comments were conveyed to the applicant. Refer to the labeling section of this review for details. The revised container labels and carton labeling, as submitted in the 06-Jun-2012 amendment, are acceptable from the CMC perspective. However, the DMEPA comments have not been conveyed to the applicant yet. Therefore, the final acceptability of the container labels and carton labeling is pending the applicant's satisfactory response to the DMEPA comments.

The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, M.S., CMC Lead, Division of New Drug Quality Assessment I
(DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

SUE CHING LIN
06/08/2012

JANICE T BROWN
06/08/2012

**Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

OND Division: Division of Hematology Products
NDA: 203565
Applicant: Luitpold Pharmaceuticals, Inc.
Stamp Date: 03-Oct-2011
PDUFA Date: 03-Aug-2012
Proprietary (Brand) Name of Drug Product: Injectafer®
Established Name: Ferric carboxymaltose
Dosage Form(s): Injection
Strength(s): (b) (4) 750 mg (b) (4) of iron (as ferric carboxymaltose).
 The applicant cross referenced the previous CMC information in NDA 22-054 (b) (4).

Route of Administration: Intravenous
Proposed Indication(s): Treatment of iron deficiency anemia
CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II: Sarah Pope Miksinski, Ph.D. /DNDQA1/ONDQA
Review team recommendation: Single reviewer
 CMC reviewers: Sue Ching Lin
 Biopharmaceutics reviewer: None

	Yes	No
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	X	<input type="checkbox"/>

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
ONDQA Biopharmaceutics	Not required as assessed by Minerva Hughes.
CDRH	Not Applicable
EA	Categorical exclusion requested
EES	Inspection request was submitted on 24-Oct-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Not requested.
Microbiology	Requested a micro reviewer to review the microbial limits in DMF 16,967 and the (b) (4) processing and (b) (4) sterilization of the drug product.
Pharm-Tox	Determined by primary reviewer.
Statistics	Determined by primary reviewer.

SUMMARY

Injectafer® (ferric carboxymaltose injection) is a sterile solution intended for intravenous use for the treatment of iron deficiency anemia. Ferric carboxymaltose is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate, having a relative molecular weight of approximately 150,000 Daltons.

On June 15, 2006, the applicant submitted NDA 22-054 indicated for the treatment of iron deficiency anemia in heavy uterine bleeding, postpartum, inflammatory bowel disease and hemodialysis patients. NDA 22-054 provided for the same drug product supplied in (b) (4). The CMC reviewer did not identify any deficiencies and recommended an approvable action pending satisfactory revisions to the labels and labeling.

On March 11, 2008 the Division issued a Not Approvable letter to the sponsor citing clinical deficiencies that remained to be resolved before the product can be approved. The sponsor submitted a response to the not approval letter for NDA 22-054 on September 15, 2011. In a September 23, 2011 teleconference, the Division notified the applicant that a new NDA is required since the indication was broadened to iron deficiency anemia. Since there were no changes to the previously submitted clinical and non-clinical information, the agency agreed to cross reference the summaries and reports submitted under NDA 22-054. CMC notified the sponsor to submit full CMC information for the new strengths.

On October 3, 2011 the applicant submitted NDA 203565 that included CMC information for (b) (4) drug product strengths. The drug product, now called Injectafer® (ferric carboxymaltose injection), will be supplied in (b) (4) 15 mL vials respectively providing (b) (4) 750 mg (b) (4) of iron (as ferric carboxymaltose). The applicant is proposing to cross reference the previous CMC information in NDA 22-054 (b) (4).

1. DRUG SUBSTANCE

1.1 Vifor Pharma provided a letter of authorization dated (b) (4) allowing the agency to reference the confidential information in DMF 16,967 for VIT-45 Powder.

1.2 NDA 22-054, CMC review #1 indicated that DMF 16,967 was previously reviewed on 16-Jan-2004 and found adequate; however, DARRTS does not list a CMC review for this DMF. (b) (4)

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/s/

JANICE T BROWN
12/02/2011

SARAH P MIKSINSKI
12/02/2011

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 203565 **Supplement Number and Type:** **Established/Proper Name:** Ferric carboxymaltose Injection

Applicant: Luitpold Pharmaceuticals, Inc. **Letter Date:** 28-Sep-2011 **Stamp Date:** 03-Oct-2011

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		Requested by the agency.
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.			N.A.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	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: <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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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		Cross referenced DMF 16,967. LOA provided.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross referenced DMF 16,967. LOA provided
14.	Does the section contain information regarding the characterization of the DS?	X		Cross referenced DMF 16,967. LOA provided
15.	Does the section contain controls for the DS?	X		Cross referenced DMF 16,967. LOA provided
16.	Has stability data and analysis been provided for the drug substance?	X		Cross referenced DMF 16,967. LOA provided
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	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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 biowaivers been requested?		X	
	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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

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

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
33.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			
34.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		
35.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		

{See appended electronic signature page}

Janice Brown, Branch II/DNDQA1/ONDQA

02-Dec-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D. /DNDQA1/ONDQA

02-Dec-2011

Comments for 74-Day Letter:

1. Submit a summary on the actual and potential product related substances including aggregates and low molecular weight iron carbohydrate complexes in the drug product arising from the degradation of the drug substance during the manufacturing and storage of the drug product. Include any changes in the molecular weight distribution, average molecular weight and particle size.
2. Provide data supporting the lack of testing for free versus bound iron in the drug product specification and during in-use testing after dilution of the drug product in sterile 0.9% sodium chloride injection, USP.
3. Since ferric carboxymaltose injection is a parenteral drug product, include a test of osmolality in the drug product specification.
4. Submit the drug product photostability test results. If photostability testing was previously

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

performed, provide the location (volume, page number) where this information can be found.

5. Resubmit pages 6 and 7 located in section 3.2.P.2.6, Appendix ZE. The headings are blacked out and can not be read.

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/s/

JANICE T BROWN
12/02/2011

SARAH P MIKSINSKI
12/02/2011