CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022150Orig1s000

CHEMISTRY REVIEW(S)

Firazyr (icatibant injection)
30 mg
NDA 22-150
Chemistry, Manufacturing, and Controls
Addendum to Division Director Memo.

Applicant: Shire Human Genetic Therapies.
500 Patriot Way
Lexington, MA 02421

Indication: Treatment of Hereditary Angioedema (HAE)
Presentation: Firazyr is supplied in a single, sterile, pre-filled, ready-to-use, 3 mL glass syringe as a single strength of 30 mg icatibant. Each single-use (b) (4) syringe is fitted with a Luer-lock and a tip cap. The carton also includes a separate 25 gauge (b) (4) needle. Firazyr is supplied in packages containing a single syringe carton or cartons of three.

EER Status:	Recommendations:	**Acceptable**
Consults:	EA –	Categorical exclusion provided
	CDRH-	Comments on ISO testing for syringe provided
	Statistics –	N/A
	Methods Validation –	May be pursued once complete characterization of the impurities are complete.
	DMETS-	Acceptable
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Previously this review indicated that the overall compliance status for manufacturing and testing facilities was pending. Recently on August 8, 2011, the Office of Compliance issued an acceptable overall recommendation for the NDA. On August 22, 2011, the office of compliance revised its recommendation to withhold due to GMP issues observed during routine surveillance inspection at one of the analytical testing sites (b) (4) This site was responsible for the drug substance bioburden and bacterial endotoxin content.

During a teleconference with the applicant, Shire indicated that they had identified an alternate testing site (b) (4) for the above testing responsibilities. Shire has subsequently amended the NDA withdrawing the (b) (4) site and indicating that (b) (4) would perform the required bioburden and endotoxin testing. This information has been entered into EES and the Office of compliance has issued an overall acceptable recommendation for the application.

Note that the applicant indicated that they would like to release drug substance and drug product tested by (b) (4) site since they had already prepared a launch stock for distribution without being aware of potential GMP issues at the (b) (4) testing site.

The Office of Compliance and ONDQA discussed this issue and agreed that under the circumstances of "Regulatory Discretion" Shire may be allowed to distribute the stocked

material that were prepared in anticipation of an approval action. The circumstances are as follows

Shire will retest the drug substance and drug product manufactured using drug substance that relied on (b) (4) as a testing site at an approved alternate testing site (b) (4)

Shire identified the lots of drug substance and drug product manufactured using material tested at the (b) (4) site and indicated that they would withdraw any product that did not pass the bioburden and bacterial endotoxin results when tested at the alternate approved site.

Based on the above conditions, ONDQA and OC will find it acceptable to distribute product that used (b) (4) as an analytical testing site. However all future drug substance and drug product will be tested at the approved testing site (b) (4)

During the course of the review cycle, a CDRH consult for the evaluation of the robustness, performance and human factors related assessment of the (b) (4) syringe and the (b) (4) (b) (4) needle was requested. CDRH reviewer, Ms. Mary Brooks, indicated in her review (dated June 15, 2011) that the current (b) (4) Syringe did not meet the international standards (b) (4) Although the results of this testing is not a requirement for an NDA, the applicant was asked to perform the ISO testing as per (b) (4) as indicated in the comment below.

Summary results from this testing was received on Friday July 29, 2011 and during the internal meeting between ONDQA and CDRH, there was verbal agreement that the summary results provided by (b) (4) for the (b) (4) syringe and (b) (4) needle that are part of the current NDA application are acceptable.

However subsequent to the internal meeting between CDRH and ONDQA, the finalized review generated by CDRH states that they would like to request further clarification from (b) (4) (b) (4) on the full study reports and would like to request a statistical basis of sampling for further bench testing. CDRH would like to request that all the bench testing be performed on 30 samples each.

ONDQA feels that this request is acceptable but will pursue with (b) (4) in their Drug Master File (b) (4) after the approval of this application. The purpose of this comment is

- to get additional bench data and information on the (b) (4) Needle to get the documentation in the DMF

- to prevent future potential incompatibilities between (b) (4) Syringes and needles not manufactured by (b) (4) for other drug products and encompasses a wider scope of issues that have been noted e.g., with Adenosine and Risperdal Consta.

Conclusion:

Based on the withdrawal of the [redacted] (b) (4) site, addition of an alternate site for testing bioburden and endotoxins, and the [redacted] (b) (4) Syringe documentation request plan, ONDQA can recommend that the drug product is satisfactory.

Additional Items:
All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. The method validation package will be sent, as needed, to FDA laboratories upon conclusion of review.

Overall Conclusion:
From a CMC perspective, the application is recommended for **approval.**

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/s/

ERIC P DUFFY
08/24/2011
Addendum to CMC Div Dir Review

Firazyr (icatibant injection)
30 mg
NDA 22-150
Chemistry, Manufacturing, and Controls
Division Director Memo.

Applicant: Shire Human Genetic Therapies.
500 Patriot Way
Lexington, MA 02421

Indication: Treatment of Hereditary Angioedema (HAE)
Presentation: Firazyr is supplied in a single, sterile, pre-filled, ready-to-use, 3 mL glass syringe as a single strength of 30 mg icatibant. Each single-use (b) (4) syringe is fitted with a Luer-lock and a tip cap. The carton also includes a separate 25 gauge (b) (4) t needle. Firazyr is supplied in packages containing a single syringe carton or cartons of three.

EER Status:	Recommendations:	**Pending**
Consults:	EA –	Categorical exclusion provided
	CDRH-	Comments on ISO testing for syringe provided
	Statistics –	N/A
	Methods Validation –	May be pursued once complete characterization of the impurities are complete.
	DMETS-	Acceptable
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Phase 4 Agreements/Commitments/Requirements

1. The applicant has committed to provide the following information by September 2012.
   a. The structures for all the unspecified impurities observed at (b) (4) in the drug product stability studies;
   b. The structures or at least "minimal structural information" for all the unspecified impurities observed at (b) (4) in the drug product stability studies.

2. The applicant proposed to revisit the current acceptance criterion (b) (4)) for impurity designated as (b) (4) which has been identified as (b) (4) in the drug substance, as more manufacturing experience is gained and complete the reevaluation by first quarter in 2012 (March 2012).

3. In order to ensure that exposures of residual (b) (4) remain as low as reasonably achievable, Shire commits to evaluate suitable manufacturing process control strategies such as an action or alert limit to complement the specifications for these heavy metals in the drug substance. Based on the limited manufacturing data available at this time, Shire commits to this evaluation upon production of a sufficient number (b) (4) of independent drug

substance batches. This evaluation and implementation will be complete by fourth quarter of 2013 if indicated.

4. Shire agrees to revise the post approval stability protocol to include testing for purity and impurities testing by HPLC methods I and II at the 3 and 9 month time points starting with the 2011 annual stability commitment batch.

Drug Substance:
Icatibant acetate is a New Molecular Entity (NME). It is a synthetic decapeptide analogue of naturally-occurring bradykinin. The chemical name of icatibant acetate is D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]–L-arginine, acetate salt. The molecular formula for the (b) (4) peptide is $C_{59}H_{89}N_{19}O_{13}S$ with a molecular weight of 1304.55. (b) (4)

Icatibant acetate is characterized as a white to almost white powder. The peptide is freely soluble in water, isotonic saline, phosphate buffer (pH 7.4), acetate buffer (pH 3.5), (b) (4) ethanol, and methanol.

The structure of icatibant was elucidated using a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), elemental analysis, infrared spectrophotometry (IR), ^{1}H and ^{13}C nuclear magnetic resonance spectrometry (NMR), gas chromatography mass spectrometry (GC-MS), and electrospray ionization - mass spectrometry (ESI-MS).

Reference is made to DMF (b) (4) for information on the chemistry, manufacturing and controls of the drug substance. Solid-phase peptide chemistry is used to synthesize icatibant. The drug substance is manufactured by (b) (4). This site was found acceptable by the office of compliance.

The proposed release specification for drug substance includes appearance, appearance of solution, identification (ESI-MS, IR, reverse phase high performance liquid chromatography (RP-HPLC) and AAA), specific optical rotation, individual peptide-related impurities and total peptide-related impurities by RP- HPLC, assay by RP-HPLC, water content by Karl Fischer, acetate content, trifluoroacetate content, residual organic solvents by gas chromatography, heavy metals, bacterial endotoxins, and microbial limit.

The impurity and degradation profiles have been investigated. Primary and secondary reference standards for drug substance have been developed and extensively characterized. Stability data provided by the DMF holder support the proposed (b) (4)-month retest period for the drug substance stored at or below (b) (4)

Conclusion: Drug substance is acceptable.

Drug Product:
Firazyr is to be administered as a subcutaneous injection. Firazyr is provided in a single strength as a sterile, ready to use solution in a pre-filled [redacted] glass syringe. The product is intended to deliver 30 mg of icatibant in a 3 mL injection. Each syringe of Firazyr contains 10.00 mg/mL icatibant, [redacted] sodium hydroxide NF, [redacted] glacial acetic acid USP, [redacted] sodium chloride USP, and water for injection USP to [redacted] Each syringe is filled with 3 [redacted] mL of solution [redacted]
Manufacturing of the drug product includes [redacted]

The drug product is manufactured at [redacted]
The office of compliance has not yet provided a final recommendation for this site and the application.

The proposed release specification for drug product includes appearance, clarity and color, identification (HPLC with ultraviolet detection (UV), HPLC with diode spectral array detection (DAD)), organic impurities by HPLC, sterility by membrane filtration, bacterial endotoxins, content by HPLC, pH, osmolality, particulate matter, and uniformity of dosage units.

The proposed expiry for Firazyr is 18 months stored below 25°C (77 °F); the product must not be stored frozen. The major instability trend observed under these conditions is [redacted] The current data support the requested expiry period.

During the course of this review cycle, a CDRH consult for the evaluation of the robustness, performance and human factors related assessment of the [redacted] syringe and the [redacted] needle was requested. CDRH reviewer, Ms. Mary Brooks, indicated in her review (dated June 15, 2011) that the current [redacted] Syringe did not meet the international standards [redacted] Although the results of this testing is not a requirement for an NDA, the applicant was asked to perform the ISO testing as per [redacted] as indicated in the comment below.

Summary results from this testing was received on Friday July 29, 2011 and the review team (ONDQA and CDRH) found the results of this testing acceptable

Conclusion: Drug product is satisfactory pending **acceptable recommendation from Office of Compliance** for the manufacturing and testing facilities.

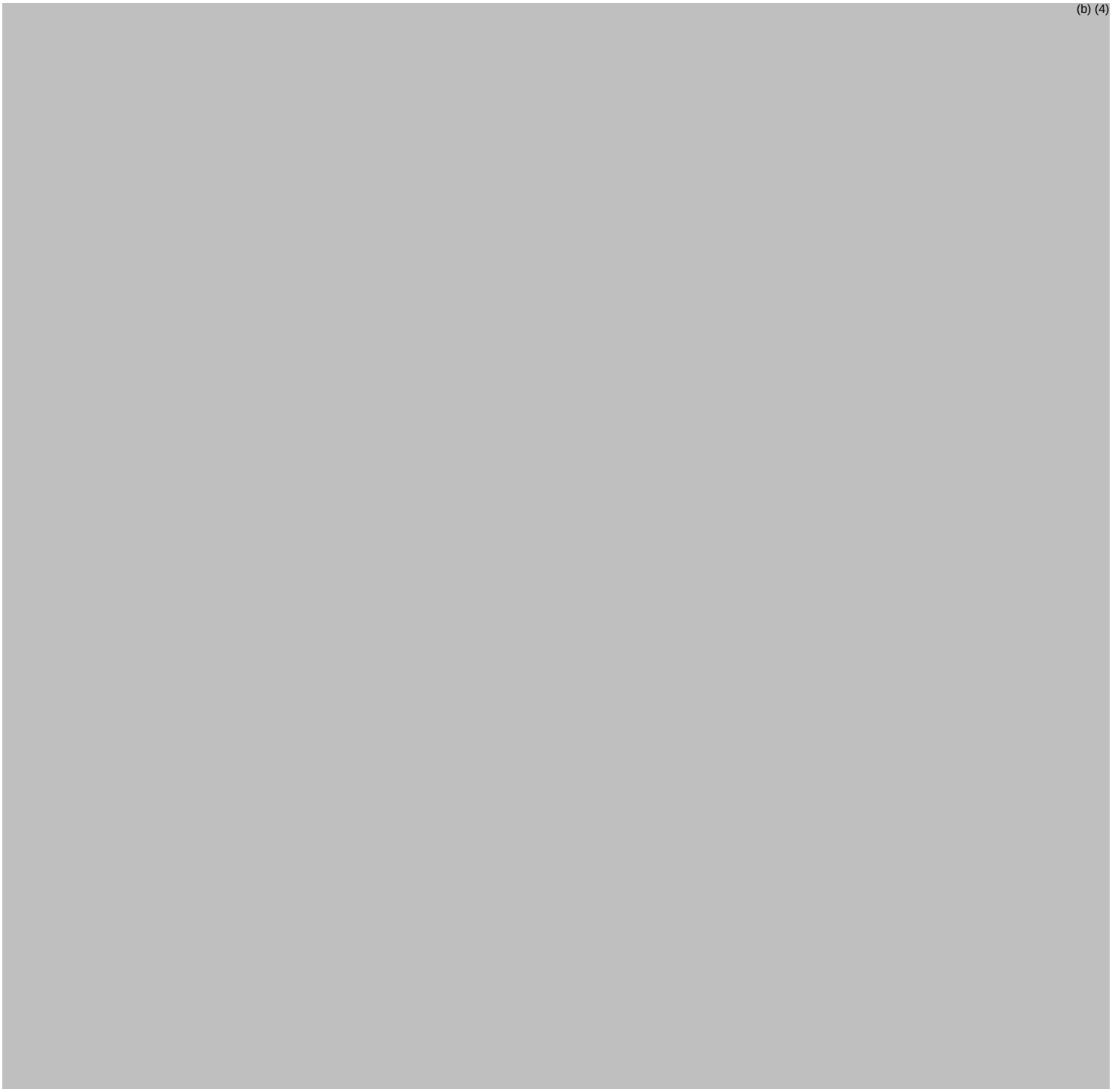
Additional Items:
All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug

product. The method validation package will be sent, as needed, to FDA laboratories upon conclusion of review.

Overall Conclusion:
From a CMC perspective, the application is recommended **approval pending evaluation of the above mentioned items.**

(b) (4)



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/s/

EUNICE H CHUNG-DAVIES
08/05/2011

ERIC P DUFFY
08/05/2011
Note that the Compliance recommendation is pending.

Firazyr
(icatibant)
Injection, 30 mg
NDA 22-150
Chemistry, Manufacturing, and Controls
CMC Secondary Review.

Applicant: **Shire Human Genetic Therapies**.
500 Patriot Way
Lexington, MA 02421

Indication: Treatment of Hereditary Angioedema (HAE)
Presentation: Firazyr is supplied in a single, sterile, pre-filled, ready-to-use, glass syringe as a single strength of 30 mg icatibant. Each single-use syringe is fitted with a Luer-lock and a tip cap, sealed in a laminated blister with a separate needle, and packed in a carton.

EER Status:	Recommendations:	**Pending**
Consults:	EA –	Categorical exclusion provided
	CDRH-	Comments on ISO testing for syringe provided
	Statistics –	N/A
	Methods Validation –	May be pursued once complete characterization of the impurities are complete.
	DMETS-	Acceptable
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Phase 4 Agreements/Commitments/Requirements

1. The applicant should provide the following information to identify the unspecified impurities in the drug product:
   a. The structures for all the unspecified impurities observed at (b) (4) in the drug product stability studies;
   b. The structures or at least "minimal structural information" for all the unspecified impurities observed at (b) (4) in the drug product stability studies.

   Since icatibant contains unnatural amino acids that may not degrade or be metabolized like natural amino acids, Pharm/Tox considers it important that the structures of the unspecified impurities be defined so that the structures can be assessed for structural alerts and/or subject to QSAR analysis (see the Pharm/Tox review dated 23-Jul-2011). The requirement is also in line with the pre-NDA agreement on impurity identification and characterization. A post-approval commitment request

has been issued to the applicant by Pharm/Tox and the applicant has committed to provide the information by September, 2012.

2. The CMC team has requested the applicant to provide bench performance testing data to demonstrate the syringe-needle compatibility as soon as possible. Given the favorable benefit/risk profile of the product, in the event that the applicant could not provide the data in time for review prior to the PDUFA date, the following recommendation for post-marketing commitment would apply:

   Provide bench performance testing data to demonstrate the compatibility between the (b) (4) (b) (4) syringe with luer lock and the (b) (4) 25G needle as used in the icatibant injection product. It is strongly suggested that the applicant conduct the testing as required under ISO (b) (4) (b) (4)

(Note that the results of the above ISO (b) (4) testing have already been provided and are being reviewed. If acceptable, this commitment may not be listed in the action letter)

3. This pertains to the impurity designated as (b) (4) which has been identified as (b) (4) in the drug substance. The applicant has proposed to retain the acceptance criterion of (b) (4) until further manufacturing experience has been gained. The applicant proposed to revisit the specification as more manufacturing experience is gained.

4. In order to ensure that exposures of residual (b) (4) remain as low as reasonably achievable, Shire commits to evaluate suitable manufacturing process control strategies such as an action or alert limit to complement the specifications for these heavy metals in the drug substance. Based on the limited manufacturing data available at this time, Shire commits to this evaluation upon production of a sufficient number (b) (4) of independent drug substance batches.

Drug Substance:

The drug substance icatibant acetate is a New Molecular Entity (NME). It is a synthetic decapeptide analogue of naturally-occurring bradykinin. The chemical name of icatibant acetate is D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]–L-arginine, acetate salt. The molecular formula for the (b) (4) peptide is $C_{59}H_{89}N_{19}O_{13}S$ with a molecular weight of 1304.55. (b) (4)

(b) (4)

Icatibant acetate is characterized as a white to almost white powder. The peptide is freely soluble in water, isotonic saline, phosphate buffer (pH 7.4), acetate buffer (pH 3.5), (b) (4) (b) (4) ethanol, and methanol.

The structure of icatibant was elucidated using a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), elemental analysis, infrared spectrophotometry (IR), ^{1}H and ^{13}C nuclear magnetic resonance spectrometry (NMR), gas chromatography mass spectrometry (GC-MS), and electrospray ionization - mass spectrometry (ESI-MS).
Reference is made to DMF (b) (4) for information on the chemistry, manufacturing and controls of the drug substance. Solid-phase peptide chemistry is used to synthesize icatibant. (b) (4)

he drug substance is manufactured by

The proposed release specification for drug substance includes appearance, appearance of solution, identification (ESI-MS, IR, reverse phase high performance liquid chromatography (RP-HPLC) and AAA), individual peptide-related impurities and total peptide-related impurities by RP- HPLC, assay by RP-HPLC, water content by Karl Fischer, acetate content, trifluoroacetate content, residual organic solvents by gas chromatography, heavy metals, bacterial endotoxins, and microbial limit. The proposed regulatory methods have been validated.
The impurity and degradation profiles have been investigated. Primary and secondary reference standards for drug substance have been developed and extensively characterized. Stability data provided by the DMF holder support the proposed (b) (4)-month retest period for the drug substance stored at or below (b) (4)

Conclusion: Drug substance is acceptable.

Drug Product:
Firazyr Injection is a parenteral drug product for subcutaneous injection that contains the drug substance (icatibant acetate), sodium acetate USP (b) (4) sodium chloride USP (b) (4) and water for injection USP. Firazyr is provided in a single strength as a sterile, ready to use solution in a pre-filled (b) (4) glass syringe. The product is intended to deliver 30 mg of icatibant in a 3 mL injection. Each syringe of Firazyr contains 10.00 mg/mL icatibant, (b) (4) sodium hydroxide NF, (b) (4) glacial acetic acid USP, (b) (4) sodium chloride USP, and water for injection USP to (b) (4) (b) (4) Each syringe is filled with 3 (b) (4) mL of solution to accommodate syringe and needle holdup volume. Manufacturing of the drug product includes formulation of drug substance with excipients, mixing, filtration of the bulk solution, filling of syringes, and (b) (4) sterilization.

The drug product is manufactured at [redacted] The office of compliance has not provided a final recommendation for this site and the application.

The proposed release specification for drug product includes appearance, identification (HPLC with ultraviolet detection (UV), HPLC with diode spectral array detection (DAD)), organic impurities by HPLC, sterility by membrane filtration, bacterial endotoxins, content by HPLC, pH, osmolality, particulate matter, uniformity of dosage units, migration products (extractables and leachables) by HPLC, slide and static friction, and loss in weight.

The proposed expiry for Firazyr is 18 months stored below 25°C (77 °F); the product must not be stored frozen. The major instability trend observed under these conditions [redacted] he current data support the requested expiry period.

During the course of this review cycle, a CDRH consult for the evaluation of the robustness, performance and human factors related assessment of the [redacted] syringe and the [redacted] needle was requested. CDRH reviewer, Ms. Mary Brooks, indicated in her review that the current [redacted] Syringe did not meet the international standards [redacted]. Although the results of this testing is not a requirement for an NDA, the applicant was asked to perform the ISO testing as per [redacted] as indicated in the comment below.

Provide bench performance testing data to demonstrate the compatibility between the [redacted] syringe with Luer lock and the [redacted] needle as used in the icatibant injection product. We strongly suggest that you conduct the testing a required under ISO [redacted] for the following parameters: [redacted]

Summary results from this testing was received on Friday July 29, 2011 and are currently being reviewed.

Conclusion: Drug product is satisfactory pending

evaluation of the ISO [redacted] results

evaluation of a late CMC amendment that was received on July 15th, 2011, and July 21st, 2011 which pertain to reanalysis of a specified impurity that was incorrectly calculated in the resubmission due to faulty analytical calculations, and

acceptable recommendation from Office of Compliance for the manufacturing and testing facilities.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. The method validation package will be sent, as needed, to FDA laboratories upon conclusion of review.

Overall Conclusion:
From a CMC perspective, the application is recommended **approval pending evaluation of the above mentioned items.**

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/s/

PRASAD PERI

08/01/2011

Approval pending EES, evaluation of ISO testing and evaluation of analytical results of impurity testing

NDA 22-150

Firazyr (icatibant) Injection
30 mg

Shire Human Genetic Therapies
(Previous applicant: Jerini US Inc.)

Yong Hu, Ph.D.

Office of New Drug Quality Assessment

for the

Division of Pulmonary, Allergy and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-150

2. REVIEW #: 2

3. REVIEW DATE: 27-Jul-2011

4. REVIEWER: Yong Hu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	06-Mar-2008
Not Approvable Action Letter	23-Apr-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete response to Not Approvable Letter	25-Feb-2011
Amendment/Draft labeling	09-May-2011
Amendment/Response to Information Request	20-May-2011
Amendment/Manufacturing facilities, methods	07-Jun-2011
Amendment/Response to Information Request	14-Jun-2011
Amendment	15-Jul-2011
Amendment	21-Jul-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Shire Human Genetic Therapies (previously Jerini US Inc.)
Address:	500 Patriot Way Lexington, MA 02421
Representative:	Thomas Class, RAC, Group Director, Regulatory Affairs
Telephone:	781-482-9130

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Firazyr

b) Non-Proprietary Name (USAN): Icatibant acetate
c) Code Name/# (ONDC only): JE049 (aka HOE140)
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Bradykinin B2 receptor antagonist for treatment of Hereditary Angioedema (HAE).

11. DOSAGE FORM: Injection solution in a prefilled syringe

12. STRENGTH/POTENCY: 10* mg/mL, 30* mg per pre-filled 3 mL syringe
(*base concentration; formulated as icatibant acetate)

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

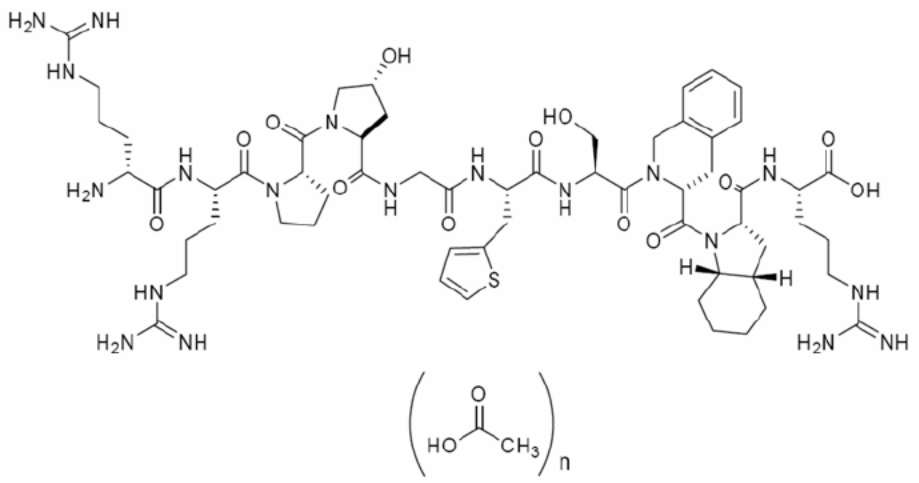
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC Three Letter Code: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate salt

Molecular Formula: $C_{59}H_{89}N_{19}O_{13}S$ (net) $C_{59}H_{89}N_{19}O_{13}S \cdot n\ CH_3COOH$ (b) (4)
Molecular Weight: 1304.55 g/mol (average, net)

IUPAC

D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]-L-arginine,
acetate salt



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	2			1	Adequate with IR letter	17-Mar-2008	The information for the key IR items was also provided in the NDA 22-150. The NDA contains adequate information for the drug substance.
	3			4	Adequate		CDRH has general concerns about (b) (4) syringe-needle compatibility based on post-marketing AEs and suggests to request bench performance testing data as required by ISO (b) (4) (Mary Brooks). The clinical team has no concerns about the syringe device from available clinical study and use data for icatibant injection. The NDA applicant (Shire) has been asked by FDA to provide bench performance testing data under ISO (b) (4)
	3			1	Adequate	02-Sept-2009 (Joel Hathaway) 07-Jul-2009 25-Jun-2008 (Yichun Sun)	

[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:

NA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Pending as of 12-Jul-2011.		
Pharm/Tox	The proposed specification of NMT (b) (4) impurities in the drug product is supported by the adequate safety margin based on the toxicology studies. The drug product leachables (b) (4) are not mutagenic. It is necessary for the applicant to provide post NDA approval the structures for the unspecified impurities observed at (b) (4) and at least minimal structural information for the unspecified impurities observed at (b) (4) bu (b) (4) in the drug product stability studies.	15-Jul-2011 (Wrap up meeting) 23-Jul-2011 (Consult review)	Hans Rosenfeldt
Biopharm	Not requested. Injectable solution formulation.		
LNC	Not requested.		
Methods Validation	Not requested. No significant change in methods since last CMC review by Dr. Eugenia Nashed.		
OPDRA	Not requested.		
EA	Adequate.	06-Mar-2008	Eugenia Nashed
Microbiology	Adequate.	02-Jun-2011	Vinayak Pawar
CDRH	CDRH recommends to request the following additional information from the applicant: 1) Due to postmarket adverse events with (b) (4) glass syringes, provide bench performance testing (e.g. ISO (b) (4) testings) demonstrating syringe to needle compatibility; 2) Provide adequate information to demonstrate that Firazyr in pre-filled syringes can be self-administered safely and effectively by patients from a human factors study in which	Email and meeting discussions . Consult review (27-Jul-2011)	Mary Brooks

	therapy is delivered by the patient and not a clinical professional. (This CMC Reviewer notes that the applicant has conducted a phase 3 clinical study to demonstrate the safety and efficacy of self-administration of the icatibant injection. The medical review by Dr. Brian Porter has determined that the clinical studies are adequate to support self-administration from safety and efficacy perspectives.)		

Chemistry Review for NDA 22-150

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for "Approval" pending an overall *acceptable* recommendation from the Office of Compliance on the manufacturing and testing facilities.

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

1. The applicant should provide the following information to identify the unspecified impurities in the drug product:
    a. The structures for all the unspecified impurities observed at (b) (4) in the drug product stability studies;
    b. The structures or at least "minimal structural information" for all the unspecified impurities observed at (b) (4) in the drug product stability studies.

    Since icatibant contains unnatural amino acids that may not degrade or be metabolized like natural amino acids, Pharm/Tox considers it important that the structures of the unspecified impurities be defined so that the structures can be assessed for structural alerts and/or subject to QSAR analysis (see the Pharm/Tox review dated 23-Jul-2011). The requirement is also in line with the pre-NDA agreement on impurity identification and characterization. A post-approval commitment request has been issued to the applicant by Pharm/Tox and the applicant has committed to provide the information by September, 2012.

2. The CMC team has requested the applicant to provide bench performance testing data to demonstrate the syringe-needle compatibility as soon as possible. Given the favorable benefit/risk profile of the product, in the event that the applicant could not provide the data in time for review prior to the PDUFA date, the following recommendation for post-marketing commitment would apply:

    Provide bench performance testing data to demonstrate the compatibility between the (b) (4) (b) (4) syringe with luer lock and the (b) (4) 25G needle as used in the icatibant injection product. It is strongly suggested that the applicant conduct the testing as required under ISO (b) (4) (b) (4)

3. This pertains to the impurity designated as (b) (4) which has been identified as (b) (4) (b) (4) in the drug substance. The applicant has proposed to retain the acceptance criterion of (b) (4) until further manufacturing experience has been gained. The applicant proposed to revisit the specification as more manufacturing experience is gained.

4. In order to ensure that exposures of residual lead and mercury remain as low as reasonably achievable, Shire commits to evaluate suitable manufacturing process control strategies such as an

action or alert limit to complement the specifications for these heavy metals in the drug substance. Based on the limited manufacturing data available at this time, Shire commits to this evaluation upon production of a sufficient number (at least 30) of independent drug substance batches.

II. Summary of Chemistry Assessments

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

The drug substance, a synthetic deca-peptide based on the structure of bradykinin is a new molecular entity (NME). The drug product is comprised of (b) (4) solution of the peptide (10 mg/mL), pre-filled in 3 mL syringes. It is indicated for the treatment of Hereditary Angioedema (HAE).

Drug substance

The drug substance, icatibant acetate (JE049, also known as HOE140), is a synthetic deca-peptide based on the structure of nona-peptide hormone bradykinin. It is an effective bradykinin type 2 receptor antagonist. It is manufactured by a (b) (4) (b) (4) – see structure on page 5.

The drug substance is an acetate salt, and is freely soluble (b) (4) (b) (4)

The drug substance is (b) (4) It has a retest period of (b) (4) (b) (4)

Drug Product

FIRAZYR is provided as a sterile, isotonic, and buffered solution of icatibant acetate in a single-use, prefilled syringe for subcutaneous administration. Each mL of the solution contains 10 mg of icatibant (free base). Each prefilled syringe delivers 3 mL of solution equivalent to a 30 mg icatibant dose. The solution is clear and colorless. The solution also contains sodium chloride, glacial acetic acid, sodium hydroxide and water for injection with a pH of approximately 5.5.

The primary packaging components in immediate contact with the drug product form a container closure system consisting of a syringe (clear type I glass) with plunger stopper (b) (4) and a Luer-lock adaptor (b) (4) These components are produced by (b) (4) (b) (4).

The secondary packaging for the single pack size consists of (b) (4) (b) (4)

The secondary packaging for the multi pack consists of (b) (4)

Manufacturing of the commercial drug product is carried out by (b) (4) (b) (4) The Phase 3 pivotal clinical batches included the glass ampoule and pre-filled syringe batches. The glass ampoule batches were manufactured at (b) (4) and pre-filled syringe pivotal batches were manufactured at the commercial site. All phase 3 pivotal batches were the same formulation as the proposed commercial product.

The currently proposed expiration dating period is 18 months for drug product stored (b) (4) without freezing. The proposed storage conditions and expiration dating period are supported by the submitted data. The key stability-limiting factor is the sum of total degradation products. The CMC team has requested the labeled storage condition to be revised with a temperature range, i.e., "Store between 2 - 25°C (36 – 77° F)", in response to DMEPA's concern about lack of clarity on the storage temperature in the labeling.

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

FIRAZYR is a bradykinin B2 receptor antagonist indicated for treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older. The recommended dose of FIRAZYR is 30 mg administered by subcutaneous injection in the abdominal area. Additional doses may be administered at intervals of at least 6 hours if response is inadequate or if symptoms recur. No more than 3 doses may be administered in any 24 hour period. Patients may self-administer FIRAZYR upon recognition of symptoms of an HAE attack after training under the guidance of a healthcare professional.

The proposed storage conditions for drug product are as follows: (b) (4) and do not freeze." The CMC team has requested the labeled storage condition to be revised with a temperature range, i.e., "Store between 2 - 25°C (36 – 77° F)." An expiration dating period of 18 months is considered acceptable by this reviewer for the drug product stored between 2 - 25°C (36 – 77° F).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has submitted adequate responses to address the CMC/Microbiology deficiencies stated in the not-approvable letter.

In response to a consult request for the syringe device, CDRH raised general concerns about (b) (4) syringes pertaining to syringe-needle incompatibility based on the post-marketing AEs from products with (b) (4) syringes. CDRH suggested that the applicant should conduct bench performance testing to demonstrated the syringe-needle compatibility by following (b) (4) The clinical review of the available clinical study and use data has not identified any issues leading to a concern about syringe-needle incompatibility for the icatibant injection product (communicated at the Wrap-up meeting). The CMC team has requested the applicant to provide bench performance testing data to demonstrate the syringe-needle compatibility for icatibant injection as soon as possible, which the applicant has agreed to. Given no immediate concerns of syringe device failure from the clinical review team and given the uncertainty about the relevance of the post-marketing AEs to the specific syringe-needle configuration as used in icatibant injection , this reviewer would recommend approval of this NDA based on the favorable benefit/risk profile of the product. The risk of syringe-needle incompatibility will be reassessed once the bench performance data is submitted.

III. Administrative

A. Reviewer's Signature

Electronic signature in DARRTS.

B. Endorsement Block

Electronic signatures in DARRTS.

C. CC Block

See DARRTS.

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/s/

YONG HU
07/27/2011

ALAN C SCHROEDER
07/27/2011
I concur. I'm signing for Dr. Prasad Peri.

Public Health Service
DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

DATE: Mar 24, 2008

TO: Division File System

FROM: Prasad Peri, Ph.D,

SUBJECT: CMC Amendment to include Pharmtox comment.

Drs. Prasad Peri and Eugenia Nashed requested a safety assessment of the impurity specifications proposed in the icatibant drug substance and drug product under the paradigm of the recommendations made during the TIDES Conference 2005. Additionally, review of the qualification studies referenced in the Chemistry, Manufacturing and Controls module of the NDA (section 3.2.S.3.2.3.3, -4.2, and -4.3 (bridging toxicology) was requested.

(b) (4)

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/s/

Prasad Peri
3/24/2008 04:09:18 PM
CHEMIST

Ali Al-Hakim
3/25/2008 11:47:50 AM
CHEMIST

Firazyr
(icatibant)
Injection, 30 mg

NDA 22-150

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Jerini US Inc.
55 Madison Avenue
Morristown, NJ 07960

Indication: Treatment of Hereditary Angioedema (HAE)

Presentation: Firazyr is supplied in a single, sterile, pre-filled, ready-to-use, glass syringe as a single strength of 30 mg icantibant. Each single-use syringe is fitted with a Luer-lock and a tip cap, sealed in a laminated blister with a separate needle, and packed in a carton.

EER Status: **Pending**

Consults: Pharm/Tox **Approvable** 14-MAR-2008
Microbiology **Approvable** 10-MAR-2008
EA – Categorical exclusion granted under 21 CFR §25.31(b)

Original Submission: 26-OCT-2007

Post-Approval Agreements: **None**

Drug Substance:

The drug substance icatibant acetate is a New Molecular Entity (NME). It is a synthetic decapeptide analogue of naturally-occurring bradykinin. The chemical name of icatibant acetate is D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-Lseryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2- ylcarbonyl] -L-arginine, acetate salt. The molecular formula for the (b) (4) peptide is $C_{59}H_{89}N_{19}O_{13}S$ with a molecular weight of 1304.55. (b) (4)

(b) (4)

Icatibant acetate is characterized as a white to almost white powder. The peptide is freely soluble in water, isotonic saline, phosphate buffer (pH 7.4), acetate buffer (pH 3.5), (b) (4), ethanol, and methanol.

The structure of icatibant was elucidated using a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), elemental analysis, infrared spectrophotometry (IR), ^{1}H and ^{13}C nuclear magnetic resonance spectrometry (NMR), gas chromatography mass spectrometry (GC-MS), and electrospray ionization - mass spectrometry (ESI-MS).

Reference is made to DMF (b) (4) for information on the chemistry, manufacturing and controls of the drug substance. Solid-phase peptide chemistry is used to synthesize icatibant (b) (4)

The proposed release specification for drug substance includes appearance, appearance of solution, identification (ESI-MS, IR, reverse phase high performance liquid chromatography (RP-HPLC) and AAA), individual peptide-related impurities and total peptide-related impurities by RP- HPLC, assay by RP-HPLC, water content by Karl Fischer, acetate content, trifluoroacetate content, residual organic solvents by gas chromatography, heavy metals, bacterial endotoxins, and microbial limit. The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Primary and secondary reference standards for drug substance have been developed and extensively characterized.

Stability data provided by the DMF holder support the proposed (b) (4)-month retest period for the drug substance stored at or below (b) (4)

Conclusion: Drug substance is unacceptable.

- The drug substance specification needs to include full impurity profile.
- Proposed acceptance criteria for individual and total impurities need to be justified to reflect manufacturing experience.
- Stability protocol needs to include full specification and stability commitment.

Drug Product:

Firazyr Injection is a parenteral drug product for subcutaneous injection that contains the drug substance (icatibant acetate), sodium acetate USP (b) (4), sodium chloride USP (b) (4), and water for injection USP. Firazyr is provided in a single strength as a sterile, ready to use solution in a pre-filled glass syringe. The product is intended to deliver 30 mg of icatibant in a 3 mL injection.

Each syringe of Firazyr contains 10.00 mg/mL icatibant, (b) (4) sodium hydroxide NF, (b) (4) glacial acetic acid USP, (b) (4) sodium chloride USP, and water for injection USP to (b) (4). Each syringe is filled with 3 (b) (4) mL of solution (b) (4)

Manufacturing of the drug product includes [redacted] (b) (4) Leachables and extractables are being tested until adequate manufacturing experience is accumulated.

The proposed release specification for drug product includes appearance, identification (HPLC with ultraviolet detection (UV), HPLC with diode spectral array detection (DAD)), organic impurities by HPLC, sterility by membrane filtration, bacterial endotoxins, content by HPLC, pH, osmolality, particulate matter, uniformity of dosage units, migration products (extractables and leachables) by HPLC, slide and static friction, and loss in weight.

The proposed expiry for Firazyr is 18 months stored below [redacted] (b) (4) the product must not be stored frozen. The major instability trend observed under these conditions is [redacted] (b) (4) The current data do not support the requested expiry period. It is recommended that the storage conditions be revised to storage at 2-8 °C (36-46 °F) because of positive genotoxicity results when testing degradation products.

Conclusion: Drug product is unsatisfactory.

- Impurities need be identified, qualified, and specified. Current PharmTox data do not support qualification for the proposed limits.
- Testing for leachables and extractables needs to be specified.
- Stability data need to be provided to support the requested expiry.
- *In vitro* biological activity of the peptide needs to be assessed.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. The method validation package will be sent, as needed, to FDA laboratories upon conclusion of review.

Overall Conclusion:

From a CMC perspective, the application is recommended **Approvable.**

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
3/17/2008 05:23:53 AM
CHEMIST

NDA 22-150

Firazyr (icatibant) Injection, 30* mg

(b) (4)

Jerini US Inc.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division I

Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-150

2. REVIEW #: 1

3. REVIEW DATE: 6-Mar-2008

4. REVIEWER: Eugenia M. Nashed

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Stamp Date	Assigned Date
Original NDA	26-Oct-2007	26-Oct-2007	21-Dec-2007
Amendment BC	18-Jan-2008	18-Jan-2008	22-Jan-2008
Amendment BZ	20-Feb-2008	20-Feb-2008	03-Mar-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Jerini US Inc.

Address: 55 Madison Ave., Morristown, NJ 07960 Tel: (973) 285-3274

Representative: Target Health Inc., 261 Madison Ave., 24th Floor, New York, NY 10016

Telephone: (212) 681-2100 Fax: (212) 681-2105

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Firazyr
b) Non-Proprietary Name (USAN): Icatibant acetate INN: Icatibant
c) CAS Registry Numbers: 138614-30-9 (Icatibant Acetate) and 130308-48-4 (Icatibant)
d) Code Name/# (ONDC only): JE049 (also known as HOE140)
e) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

PHARMACOL. CATEGORY: Anti-inflammatory. Bradykinin antagonist for treatment of Hereditary Angioedema (HAE).

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10* mg/mL, 30* mg per pre-filled 3 mL syringe (b) (4)

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: __x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

IUPAC Three Letter Code: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate salt

Molecular Formula: $C_{59}H_{89}N_{19}O_{13}S$ (net) $C_{59}H_{89}N_{19}O_{13}S \cdot n\ CH_3COOH$ (b) (4)
Molecular Weight: 1304.55 g/mol (average, net)

IUPAC

D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]-L-arginine,
acetate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	2			1	Adequate; IR letter	Mar 9, 2008 Prasad Peri	IR letter will be sent to Holder in Mar 2008

(b) (4)	3	(b) (4)	1	Adequate	Feb 5, 2008 Marla Stevens-Riley, Micro Rev.	(b) (4) as deficient (Micro issues) until amendment dated Jan 15, 2008.
	3		1	Adequate, IR letter dated Apr 11, 2007 was sent to the Holder	Apr 12, 2007 (b) (4) Nov 14, 2005 (b) (4) (b) (4) May 24, 2004 (b) (4) (b) (4)	(b) (4) is not in contact with drug product formulation, according to information in DMF. No response to the IR letter is provided yet.

[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 Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
	(b) (4)	Icatibant acetate	Pending		Referenced for this NDA.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EES	GMP Inspections	Nov 2007	Pending	2 sites are assigned for inspection, 2 inspections (drug product and drug substance manufacturing) are pending
Pharm/Tox		Nov 2007 Jan 23, 2008	Pending	Qualifications studies, Bridging Toxicology (3.2.S.3.2.3.3, -4.2, and -4.3) & Leachables
Biopharm				
DMETS		Nov 2007	Pending	
Methods Validation				Will be initiated as needed after the final review
DDMAC	Labeling	Nov 2007	Pending	
EA	None			Exception requested based on 21 CFR 25.31(b)
Microbiology	(b) (4)	Dec 21, 2007	AE Mar 10, 2008	Review (Anastasia Lolas) identified 9 deficiencies

The Chemistry Review for NDA 22-051

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable (AE) from a CMC perspective, pending satisfactory outcome of the outstanding issues as follow.

- Mid-cycle CMC comments were forwarded to the applicant in letter dated Jan 8, 2008. The submissions dated Jan 18, and Feb 20, 2008, are evaluated in this review. All CMC comments remaining after the evaluation of applicant's responses are listed at the end of this review, and need to be adequately addressed prior to the approval of the application.

- The EER for this NDA is currently pending. Two analytical establishments (b) (4) are assigned for inspection, and inspections are currently pending at the drug product (b) (4) and drug substance (b) (4) manufacturing sites. Overall acceptable GMP status will be needed for all manufacturing and testing facilities before the approval.

- Microbiology consult review identified several deficiencies which include lack of container-closure integrity study, lack of sterility assurance information for the 25G needle, lack of the re-qualification program for the (b) (4), lack of description of the microbiological environmental monitoring program, and (b) (4) Nine comments from the Microbiology team need to be forwarded to the applicant.

- PharmTox consult is pending (Qualification of impurities, Bridging studies for Phase 3 changes, Leachables). Based on the information presented at the Team wrap-up meeting on Mar 12, 2008, one of the degradation products (b) (4) tested positive for genotoxicity in the *in vitro* mammalian chromosome aberration test. All comments resulting from the PharmTox consult review need to be included in the action letter.

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

None.

II. Summary of Chemistry Assessments

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

The drug substance, a synthetic deca-peptide based on the structure of bradykinin is a new molecular entity (NME). The drug product is comprised of a (b) (4) solution of the peptide (10 mg/mL), pre-filled in 3 mL syringes. It is proposed for the treatment of Hereditary Angioedema (HAE).

Drug substance

The drug substance, Icatibant acetate (JE049, also known as HOE140), is a synthetic deca-peptide based on the structure of nona-peptide hormone bradykinin. It is an effective bradykinin B2 receptor antagonist. (b) (4)

(b) (4)

Drug Product

The drug product consists of a sterile solution of icatibant acetate (synthetic peptide) in pre-filled 3 mL syringe. It is intended for subcutaneous injection in treatment of attacks of hereditary angioedema (HAE). The injection solution contains icatibant acetate in concentration of 10 mg/mL (calculated as a free base, icatibant), water for injection buffered at pH 5.5 with acetic acid - sodium hydroxide, and sodium chloride added (b) (4).

The product is presented as a single-dose glass syringe pre-filled with 3 (b) (4) mL of drug product solution to deliver 30 mg (3.0 mL) of icatibant base. (b) (4)

Manufacture, packaging and testing of the commercial drug product are carried by (b) (4) (b) (4). Phase 3 batches, packaged in glass ampoules, were manufactured at (b) (4), and earlier clinical batches were manufactured at (b) (4)

The currently proposed expiry period is 18 months for drug product stored at/below 25°C (77°C), do not freeze, and protect from light. The proposed storage conditions and expiry period are not supported by the submitted data. In addition, (b) (4) one of the degradants (b) (4) tested positive for genotoxicity in the *in*

vitro mammalian chromosome aberration test. This reviewer strongly recommends storage in the refrigerator, (b) (4)

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

The drug product, Icatibant acetate Injection, 30 mg/3 mL is a sterile isotonic solution, supplied in a pre-filled 3 mL syringe pack. It is proposed for the treatment of Hereditary Angioedema (HAE) in patients 18 years and older, as once-daily subcutaneous injection.

The proposed storage conditions for drug product are: (b) (4) This reviewer requests storage in the refrigerator, and protection from light.

C. Basis for Approvability or Not-Approval Recommendation

Based on the information and data provided in this submission, the application is approvable, from a CMC perspective. The approval will be recommended when the applicant addresses adequately all deficiency comments outlined at the end of this review, and deficiencies resulting from Microbiology and PharmToxicology consult reviews. Also, an acceptable (AC) GMP status is required for all manufacturing and testing facilities supporting this application, before the approval. The EER for this NDA is currently pending. As of Mar 10, 2008, two contract drug substance testing facilities (b) (4) are assigned for inspection, and the inspection is pending at the drug substance and drug product manufacturing sites.

See below, a summary of the more important CMC deficiencies remaining to be addressed by the applicant.

- **Inadequate Controls for Drug Substance.**

The drug substance specifications need to be revised to include full impurity profile. The proposed acceptance criteria do not meet Agency recommendations for peptides (TIDES conference 2005), i.e., each impurity at, or above (b) (4) need to be identified, characterized, and qualified, and each impurity at, or above (b) (4) need to be fully identified and characterized, with at least minimal identification expected for impurities at, or above (b) (4) Evaluation of the proposed qualification is pending by the PharmTox team.

- **Inadequate Controls for Drug Product.**

The drug product specifications lack controls for biological activity, full impurity profile, testing for leachables, loss in weight, slide and static friction. The stability protocols need to be revised and resubmitted.

- **Deficient Microbiology Controls for Drug Product.**

Lack of container-closure integrity study, lack of sterility assurance information for the 25G needle, lack of the re-qualification program for (b) (4), lack of description of

the microbiological environmental monitoring program, and (b) (4) See Micro review dated Mar 10, 2008.

- **Revision of the requested storage conditions and/or expiry period for the drug product.**

The proposed storage conditions and expiry period are not supported by the submitted stability data. The currently proposed expiry period is 18 months for drug product stored at/below 25°C (77°C), do not freeze (b) (4) This reviewer strongly recommends storage in the refrigerator, (b) (4)

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III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

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/s/

Eugenia Nashed
3/13/2008 01:37:37 PM
CHEMIST

Ali Al-Hakim
3/13/2008 01:58:47 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 22-150
Applicant: Jerini US Inc.
Stamp Date: 26-Oct-2007
PDUFA Date: 26-April-2008 (will change if decided that this is priority)
Proposed Proprietary Name: Firazyr
Established Name: Icatibant
Dosage form and strength: Subcutaneous Injection, 30 mg Solution
Route of Administration: Subcutaneous Injection
Indications: Treatment of Hereditary Angioedema (HAE) including cutaneous, abdominal and laryngeal attacks.
PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA
Fileability recommendation: Acceptable for filing
Review team recommendation: Primary reviewer: Jean Nashed, Ph.D.
Time goals:

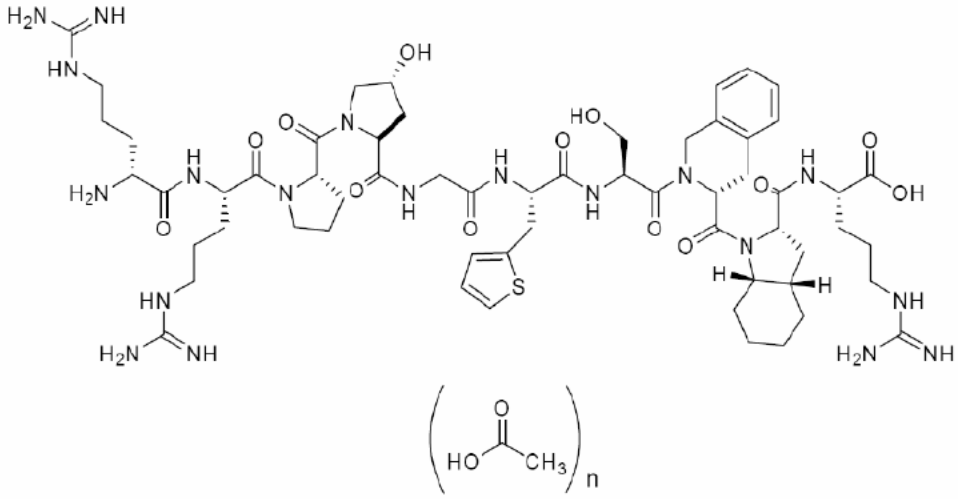
Initial Quality Assessment in DFS: by 18-Dec-2007 (NDA accessible on 2-Nov-2007)
Chemistry filing memo in DFS: by 18-Dec-2007
Filing decision "Day 60": **18-Dec-2007** (tentative; to be set by Clinical Division)
74 Day letter Due: 08-Jan-2008 (tentative; to be set by Clinical Division)
Chemistry Review (DR/IR) letter: by 23-Jan-2008 !(tentative)
Mid-cycle meeting "Month 3": 23-Jan-2008 (set by Clinical Division)
Advisory Committee Meeting: February 20, 2008
Full Labeling Meeting: February 25, 2008
Wrap-up: March 11, 2008
Labeling Tcon: March 12, 2008
Final Chemistry Review "Month 5" in DFS: by 26-Mar-2008
PDUFA: 26-April-2008

Related Documents

INDs pertaining to this are: (b) (4),

(b) (4)

USAN/INN/JAN	Icatibant acetate (USAN), Icatibant (INN)	
Chemical Name	D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]-L-arginine, acetate salt	
CAS #	138614-30-9 (Icatibant acetate)	130308-48-4 (Icatibant)
Molecular Formula	$C_{59}H_{89}N_{19}O_{13}S$ (net) · (b) (4) CH_3COOH (b) (4)	
Molecular weight	1304.55 g/mol (average, net)	
	(b) (4)	

Structure	
CONSULTS/ CMC RELATED REVIEWS	**COMMENT**
Clinical Pharm (BA/BE) - Dissolution	Not applicable
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer
EES	EES for all 4 sites listed were sent out on Nov. 19, 2007 (b) (4) (b) (4) Both the (b) (4) sites are found acceptable based on profile. The (b) (4) sites have been scheduled for inspected.
DMETS/DDMAC	Consensus is pending.
Methods Validation	To be sent when appropriate
Microbiology	Sterility and Endotoxin limits to be evaluated. Sterilization Process and Manufacturing to be evaluated.
Pharm/Tox	Consult on impurities should be requested and to be evaluated by pharmtox. Note the Agency agreed to the limits proposed at the "TIDES Conference 2005" for proteins and peptides.
Biometrics	To be decided by the reviewer

Summary:

- This is a 6 month NDA (priority) electronic NDA in CTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary (~36 pages). This NDA is filed as a 505(b) 1 application.
- This is classified as a new molecular entity as per MaPP 7500.
- The synthetic decapeptide icatibant has a structure similar to that of the hormone bradykinin and is an effective bradykinin type 2 (B2) receptor antagonist.

Drug Substance

- The drug substance is a white to almost white amorphous powder. Stoichimetrically between 1 and 4 moles of acetic acid may be present. It is hygroscopic. Icatibant acetate is freely soluble in water, isotonic saline, phosphate buffer (pH 7.4), acetate buffer (pH 3.5), (b) (4) ethanol, and methanol.
- The proposed commercial to be marketed drug substance is manufactured by (b) (4) and referenced in DMF (b) (4) (A letter of authorization for the DMF is provided). Note that the drug substance used in early clinical studies was made by (b) (4) and the drug product was packaged glass ampoules. The current manufacturing process is a (b) (4)

(b) (4) (b) (4) Type III glass bottles

- The original batches of icatibant acetate drug substance were manufactured in 1989 by a different manufacturer, namely (b) (4) In 1990 (b) (4) batches were manufactured at (b) (4) in a laboratory scale and in pilot plant scale. then decided to pursue only the (b) (4). Batches used for nonclinical and early clinical studies were manufactured employing the (b) (4). In December 2003, manufacture was transferred to (b) (4) which employs a validated (b) (4) process.
- The following attributes are provided for in the DS: Appearance, Appearance of solution, ID by (ESI Mass Spec, IR, HPLC, and Amino Acid Analysis), Related Substance, Assay, (b) (4) Acetic acid content, (b) (4) (b) (4), (b) (4), Heavy metals, Bacterial Endotoxins and Microbial Limits. Related substances include (b) (4) Note that adequate Tox evaluation on the impurities need to be done via a tox consult. (b) (4)
- Stability of the drug substance was performed as per Q1A(R2) and Q1B. When stored at -15°C for 24 months, no significant degradants were noted. However, the drug substance is very susceptible to (b) (4) It should be labeled accordingly. The recommended storage condition is (b) (4) and a retest period of (b) (4) months is noted.

Drug Product

- Icatibant 30 mg solution for injection is a parenteral drug product for subcutaneous administration. It is presented as a sterile, isotonic and buffered solution. The formulation consists of 10.0 mg/mL icatibant (free base) in water for injection, buffered at pH 5.5 with acetic acid and sodium hydroxide with sodium chloride (b) (4). No preservatives are added. (b) (4)
- Drug product is shown below.

Table 1: Unit Formula

Ingredient	Quantity per mL	Function	Reference to Standards
Active Ingredient			
Icatibant*	10.00 mg	Active ingredient	In-house
Other Ingredients	(b) (4)		
Sodium hydroxide			NF / Ph. Eur.
Glacial acetic acid			USP / Ph. Eur.
Sodium chloride			USP / Ph. Eur.
Water for Injection			USP / Ph. Eur.
(b) (4)			

- The specifications for the drug product list Appearance, Clarity and Coloration, ID (HPLC and UV), Organic Impurities, Sterility, Bacterial Endotoxins, Content, pH, Osmolality, (b) (4) and Uniformity of Dosage Units. Additional tests being performed on the primary stability batches are Migration product (b) (4) by HPLC possibly as leachables), (b) (4) (b) (4)

- A summary of the data generated from three commercial scale batches of product produced at (b) (4), the proposed manufacturer of the drug product. Primary stability data (including 12 months for the recommended storage conditions) are presented for these batches.
- Applicant proposes a shelf life of 18 months.
- The product summary is supplemented with information from three exploratory, pilot scale batches of pre-filled syringes containing the proposed commercial formulation produced on a temporary syringe filling line at (b) (4). Supporting stability data (24 months) are presented. In addition, three recent batches of the commercial formulation produced at (b) (4) and packaged in ampoules are considered also as representative of the clinical trial formulation. Further supportive stability data (30 months) are generated from these batches.
- **Container closure system.**

The drug product is packaged to deliver 3.0 mL of solution in a container closure system consisting of a syringe (clear type I glass) with grey plunger stopper (b) (4) with a Luer-lock adaptor (b) (4) with screw tip cap and white (b) (4) backstop. The pack size is one blister pack containing one pre-filled syringe and one needle (25G, (b) (4) packed separately in a cardboard box. These components are produced by (b) (4) and are referenced in a DMF (b) (4)

CRITICAL ISSUES

- **Pharmaceutical development**

Compatibility studies for the formulation, buffer, pH, suitability of the primary packaging components, performance testing (slide and static friction of pre-filled syringe) and leachables were performed.

- Leachable profiles for (b) (4) syringe components (b) (4) and two alternate plunger stopper formulations (b) (4) Note that the leachables studies were performed on (b) (4) syringes whereas the to-be marketed drug product is a 3 mL syringe. The difference should be considered during evaluation and leachables data in the to-be marketed drug product will need to be requested.
- **Dose Dumping**

Not applicable.

- **Microbial Testing**

Sterility and Endotoxins testing are proposed. Micro consult needs to be submitted. Information concerning the validation of the (b) (4) (b) (4) is presented in Section 3.2.P.3.5. (b) (4)

- **In-process controls**

The only proposed in process controls are appearance and pH.

- **Critical Process parameters**

The applicant indicates that during process validation the following critical parameters will be addressed in addition to routine process parameters and in-process controls: (b) (4)

- **Overage in the formulation.**

None proposed.

- **Excipients from Animal Origin.**

Reproduced from the NDA
".. the amino acid derivatives used in the manufacture of icatibant acetate are sourced from non-human / animal materials, see Module 3.2.S.3.2.3. The drug substance manufacturer maintains certificates of origin for all protected amino acids used in the manufacture of icatibant acetate".

- **OVIs in the drug Product**

Not applicable although they are in the drug substance.

- **Manufacturing differences between pilot and commercial scales.**

Note that during the development program there were several changes made to the drug product.

- Initially the drug product was a pre-filled ampoule, with the same concentration (10 mg/mL). These batches (63524G001, 63525G001, and 63526G002) were made at (b) (4) (b) (4) 30 months stability data under various conditions are provided. These are additional long term stability data.
- Following these, three pilot scale batches (72114G001, 72119G002, and 72126G003) were made that were pre-filled syringes. These were made at (b) (4) syringe batches and used the identical to be marketed formulation and CCS. 24 months data on these batches are available for stability review.
- Primary long term stability data generated from three registration batches (06251JR, 06261JR, and 06271JR) of pre-filled syringes manufactured at the proposed commercial site, manufacturing process and scale (b) (4) Twelve months of real time stability are provided for this product. The applicant states that (b) (4) In addition several analytical methods were revised during development. These are all listed as reports that will need to be compared and their validation reports evaluated.

- **GMP status of the drug substance/drug product manufacturing sites.**

The drug substance and drug product manufacturing sites are scheduled for inspection as of this review. The testing facilities have been found acceptable based on profile.

- **Safety of imprinting inks.**

Not applicable

- **Dissolution of the drug product.**

Not applicable.

- **Degradation products:**

Several degradation products have been identified and specified. Various unidentified impurities are also specified by their relative retention times. It is noted tha (b) (4) (b) (4) (b) (4) The applicant needs to address the identity of these impurities at the earliest. Note that the threshold for "minimal identification (b) (4) "fully identified and characterized (b) (4) and "fully identified, characterized and qualificatior (b) (4) are considered the regulatory for peptides and these were publicly announced in the TIDES conference 2005, by Dr. Blair Fraser. The sponsor indicates that the drug product degradants and impurities that are above the threshold for identification are being characterized and their limits are sent to (b) (4) The limit of total degradants is set at (b) (4). It is noted that none of the unidentified impurities are above the (b) (4) limit.

- **Sensitivity of product to moisture and light.**

Drug product is a solution. (b) (4)

- **Shelf life of the drug product (proposed 18 months).**

Adequate real time stability data is provided to assess the shelf life of the product. The proposed 18 months with the current limit of unidentified impurities needs to be evaluated by the reviewer. The sponsor is not including the testing of the following parameters for routine testing: Leachables (Migration products), (b) (4). The rationale needs to be evaluated. In addition note that the leachables identified may be potentially genotoxic and hence they need to be carefully evaluated. Jerini also indicates that the proposed acceptance criteria are based on limited manufacturing experience.

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Reference to DMFs and NDA
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

Draft CMC Comments for 74 day Letter

1. **Provide the identity of all impurities that appear at or above (b) (4) concentration of the drug substance. As per the current Agency thinking, all impurities above the threshold of (b) (4) should be identified and well characterized.**

2. **We note that the leachables data you have provided used a (b) (4) syringe as opposed to the 3 mL syringe which is proposed for the commercial distribution. Provide extractables and leachables data from the commercial container closure system or demonstrate with adequate data that the submitted results are representative of the expected levels of leachables in the drug product stored up to the shelf life in the proposed container closure. Note that adequate toxicological assessment will be needed for these leachables.**

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

/s/

Prasad Peri
12/21/2007 11:16:14 AM
CHEMIST
Inital Quality Assessment--Comments to be sent to Applicant

Ali Al-Hakim
12/21/2007 02:54:08 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22150/000	**Action Goal:**	
Stamp Date:	26-OCT-2007	**District Goal:**	26-JUN-2011
'ory:	25-AUG-2011		
Applicant:	SHIRE ORPHAN THERAP	**Brand Name:**	FIRAZYR SOLUTION FOR INJECTION
	300 SHIRE WAY	**Estab. Name:**	
	LEXINGTON, MA 02421	**Generic Name:**	ICATIBANT ACETATE (b) (4) (b) (4)
Priority:	1P	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	570	001; INJECTABLE; ICATIBANT ACETATE; 10MG	

Application Comment: THIS NDA (FIRAZYR) IS FOR A PEPTIDE MOLECULE THAT IS MADE (b) (4) THE DRUG PRODUCT IS A SUBCUTANEOUS INJECTION MADE IN A 3 ML PREFILLED GLASS SYRINGE (b) (4). JERINI USA IS THE NAME OF THE APPLICANT AND THE AUTHORISED AGENT IS TARGET HEALTH INC. 261 MADISON AVENUE, 24TH FLOOR, NEW YORK, NY, 10016, PH: 212 681 2100.
THE ADDRESS FOR THE APPLICANT IS 55 MADISON AVENUE, MORRISTOWN, NJ, 07960, PH: 973 285 3274.

THE APPLICANT IS REQUESTING A PRIORITY REVIEW IN THE COVER LETTER SINCE THIS IS A NME AND PURPORTS TO MEET UNMET MEDICAL NEED FOR A SERIOUS MEDICAL PROBLEM. THE AGENCY GRANTED A FAST TRACK STATUS IN JUNE 15, 2004, AS AT THAT TIME IT HAD THE POTENTIAL TO ADDRESS UNMET MEDICAL NEEDS. (on 19-NOV-2007 by P. PERI (HFD-820) 301-796-1730)

THE APPLICANT SUBMITTED RE-SUBMISSION TO COMPLETE RESPONSE LETTER ON 2/25/2011. (on 08-MAR-2011 by S. PATWARDHAN (HF-01) 301-796-4085)

FDA Contacts:				
	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	E. NASHED	Review Chemist	(HFD-820)	301-796-2410
	A. SCHROEDER	Team Leader		301-796-1749

Overall Recommendation:				
	ACCEPTABLE	on 25-AUG-2011	by D. SMITH	()
	WITHHOLD	on 22-AUG-2011	by EES_PROD	
	ACCEPTABLE	on 08-AUG-2011	by EES_PROD	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STERILITY TESTER

Establishment Comment: SYNTHETIC PREPARATION OF THE ACTIVE DRUG SUBSTANCE USING SOLID PHASE PEPTIDE SYNTHESIS, ANALYTICAL TESTING AND RELEASE TESTING FOR THE DRUG SUBSTANCE. SITE IS INDICATED AS BEING READY FOR INSEPCTION. IT WAS NOTED JUST RECENTLY THAT THE DRUG SUBSTANCE SITES, (b) (4) WERE LISTED IN THE DRUG MASTER FILE (b) (4) FOR THE DRUG SUBSTANCE (b) (4). THES FIVE SITES ARE SUPPORTING SITES THAT PERFORM IMPORTANT TESTING FOR THE DRUG SUBSTANCE. HENCE THESE SITES ARE BEING LISTED IN EES. (on 22-JAN-2008 by P. PERI (HFD-820) 301-796-1730)
ADDING THIS SITE AS THE BACTERIAL ENDOTOXIN AND MICROBIAL LIMIT TESTING SITE FOR THE DRUG SUBSTANCE. (on 24-AUG-2011 by K. SHARMA ())

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-NOV-2007				PERIP
SUBMITTED TO DO	20-NOV-2007	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
TION PERFORMED	(b) (4)		(b) (4)		BARRY.ROTHMAN
EI covered preapproval of Icatibant Acetate (b) (4). significant deviations included lack of microbial limit test validation(preparatory testing), failure to investigate out-of-trend stability data for (b) (4), ignoring out-of-trend and out-of-specification data during qualification of the gas chromatograph, inadequate process validation for Icatibant Acetate. EIR is classified OAI, recommending withhold of (b) (4) Icatibant Acetate, and recommending issuance of a warning letter. Previous EI was conducted during (b) (4), and was classified VAI. The current inspection found that deviations found during the (b) (4) inspection have been corrected. (b) (4) has submitted three FDA 483 responses, promising corrections. EIR submitted to ICT and FDA 483 to DFI.					
DO RECOMMENDATION	19-AUG-2008			ACCEPTABLE	ADAMSS
FIRM RESPONDED ADEQUATELY TO 483 DEFICIENCIES.				ADEQUATE FIRM RESPONSE INSPECTION	
OC RECOMMENDATION	19-AUG-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
SUBMITTED TO DO	09-MAR-2011	10-Day Letter			STOCKM
THIS DRUG SUBSTANCE WAS COVERED DURING THE (b) (4) INSPECTION.					
INSPECTION SCHEDULED	(b) (4)		(b) (4)		PHILPYE
DO RECOMMENDATION	16-JUN-2011			ACCEPTABLE	STOCKM
				INSPECTION	
OMMENDATION	16-JUN-2011			ACCEPTABLE	STOCKM

FDA CDER EES
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		DISTRICT RECOMMENDATION	
OC RECOMMENDATION	25-AUG-2011	ACCEPTABLE	SMITHDE
DUPLICATE MILESTONE TO REFLECT ACCEPTABILITY AFTER AMENDMENT ON 8/24		BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: THIS LAB PERFORMS IDENTIFICATION BY AMINO ACID ANALYSIS AND RESIDUAL ORGANIC SOLVENTS BY GC. (on 22-JAN-2008 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		PARALUMAN.LEONIN

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

CGMP and Pre-Approval inspections of this Control Testing Laboratory for NDA 22150/000, and NDA 22201/000,both for Icatibant Acetate (b) (4) were conducted for request of the (b) (4) District Office under FACTS #4515340. Inspections were carried out under CP7346.832, NDA Pre-Approval Inspections and CP7356.002 Drug Process Inspections.

'st E.I. of (b) (4) was classified VIA. FDA 483 was issued re: difference between analytical method] in method validation report from the actual method used by the firm during method validation. , firm responded to the FDA 483 and the firm was found acceptable as a Control Testing Laboratory.

This small modern Control Testing Laboratory offers chromatographic analysis service to its customers. The firm specializes particularly in the analysis of peptides, amino acid derivatives and other chiral substances. The responsibility (b) (4) for NDA 22150 is to identify the drug substance, Icatibant Acetate by Amino Acid Analysis and the residual organic solvent by gas chromatography. For NDA 22201 , the firm?s responsibility is the chiral amino acid analysis on the drug substance, (b) (4). Inspection did not disclose any significant findings. Two points were discussed with management at the closing of the inspection which were; 1) The setting of time frame for closing of complaints and 2) Analytical balance should be calibrated on each day of use as opposed to once a month?s practice. No FDA 483 was issued. Firm was found to have set of written procedures and controls in all its operations, with qualified and well-maintained equipment/instruments. Firm was also found to have qualified and well-trained personnel to be able to carry out identification of the drug substance by chiral amino acid analysis for NDA 22201 , (b) (4) and the identification of amino acid analysis and residual solvents b

DO RECOMMENDATION	06-SEP-2008	ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	06-SEP-2008	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	09-MAR-2011		PATWARDHAN
OC RECOMMENDATION	10-MAR-2011	ACCEPTABLE BASED ON PROFILE	SMITHDE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Establishment Comment:

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
OC RECOMMENDATION	10-MAR-2011			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: THIS LAB PERFORMS IDENTIFICATION OF THE DRUG SUBSTANCE BY ELECTROSPRAY IONIZATIION-MASS SPECTROMETRY (ESI-MS) (on 22-JAN-2008 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
SUBMITTED TO DO	09-MAR-2011	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			PHILPYE
OMMENDATION	14-APR-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	14-APR-2011			ACCEPTABLE	TOULOUSEM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Establishment Comment: SITE IS RESPONSIBLE FO THE FORMULATIION, (b) (4) ASSEMBLY, PACKAGING, AND LABELING STERILITY AND ENDOTOXIN TESTING AND RELEASE OF DRUG PRODUCT. SITE IS READY FOR INSPECTION. (on 19-NOV-2007 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-NOV-2007				PERIP
SUBMITTED TO DO	20-NOV-2007	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		ADAMSS
INSPECTION PERFORMED	(b) (4)		(b) (4)		ADAMSS
OMMENDATION	16-APR-2008			ACCEPTABLE	ADAMSS
				ADEQUATE FIRM RESPONSE	
				INSPECTION	
OC RECOMMENDATION	16-APR-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
SUBMITTED TO DO	09-MAR-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific			PHILPYE
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
DO RECOMMENDATION	08-AUG-2011			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	08-AUG-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: THIS SITE IS RESPONSIBLE FOR ALL OTEHR RELEASE TESTING. THE REGISTRATION NUMBER LISTED IN TEH NDA IS 3004908885 BUT COULD NOT BE FOUND IN THE SYSTEM. SITE IS READY FOR INSPECTION. (on 19-NOV-2007 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-NOV-2007				PERIP
OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
OC RECOMMENDATION	10-MAR-2011			ACCEPTABLE BASED ON PROFILE	SMITHDE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE RELEASE TESTER

Establishment Comment: THIS SITE IS RESPONSIBLE FOR OSMOLALITY TESTING FOR RELEASE, STERILITY AND BACTERIAL ENDOTOXINS TESTING, AND PART OF STABILTY TESTING PROGRAM. SITE IS READY FOR INSEPCTION. (on 19-NOV-2007 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-NOV-2007				PERIP
OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
OC RECOMMENDATION	09-MAR-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: THIS LAB PERFORMS (b) (4) TESTING BY INDUCTIVE COUPLED PLASMA EMISSION SPECTROSCOPY (ICP-OES)OF THE DRUG SUBSTANCE (on 22-JAN-2008 by P. PERI (HFD-820) 301-796-1730)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	09-MAR-2011				PATWARDHAN
OC RECOMMENDATION	10-MAR-2011			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	

11:23 am

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22150/000	Action Goal:	
Stamp:	26-OCT-2007	District Goal:	26-FEB-2008
Regulatory Due:	26-APR-2008	Brand Name:	FIRAZYR SOLUTION FOR
Applicant:	JERINI	Estab. Name:	INJECTION
	NO CITY, , XX	Generic Name:	ICATIBANT ACETATE
	1P		[redacted] (b) (4)
Priority:	570	Dosage Form:	(INJECTION)
Org Code:		Strength:	10 MG/ML, 3 ML/SYRINGE

Application Comment: THIS NDA (FIRAZYR) IS FOR A PEPTIDE MOLECULE THAT IS MADE BY [redacted] (b) (4). THE DRUG PRODUCT IS A SUBCUTANEOUS INJECTION MADE IN A 3 ML PREFILLED GLASS SYRINGE WITH A [redacted] (b) (4). JERINI USA IS THE NAME OF THE APPLICANT AND THE AUTHORISED AGENT IS TARGET HEALTH INC. 261 MADISON AVENUE, 24TH FLOOR, NEW YORK, NY, 10016, PH: 212 681 2100.
THE ADDRESS FOR THE APPLICANT IS 55 MADISON AVENUE, MORRISTOWN, NJ, 07960, PH: 973 285 3274.

THE APPLICANT IS REQUESTING A PRIORITY REVIEW IN THE COVER LETTER SINCE THIS IS A NME AND PURPORTS TO MEET UNMET MEDICAL NEED FOR A SERIOUS MEDICAL PROBLEM. THE AGENCY GRANTED A FAST TRACK STATUS IN JUNE 15, 2004, AS AT THAT TIME IT HAD THE POTENTIAL TO ADDRESS UNMET MEDICAL NEEDS. (on 19-NOV-2007 by P. PERI () 301-796-1730)

FDA Contacts:	C. HILL	(HFD-570)	301-796-2300	, Project Manager
	P. PERI		301-796-1730	, Review Chemist
	A. AL HAKIM		301-796-1323	, Team Leader

Overall Recommendation: ----------

Establishment: [redacted] (b) (4)

DMF No: [redacted] (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS LAB PERFORMS TESTING OF THE DRUG SUBSTANCE FOR BACTERIAL ENDOTOXINS (on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	[redacted] (b) (4)	GMP			ADAMSS

Never been inspected. Inspection date not confirmed as of 4/22

Establishment: CFN [redacted] (b) (4) FEI [redacted] (b) (4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No: [redacted] (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

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

Estab. Comment: SYNTHETIC PREPARATION OF THE ACTIVE DRUG SUBSTANCE USING SOLID PHASE PEPTIDE SYNTHESIS, ANALYTICAL TESTING AND RELEASE TESTING FOR THE DRUG SUBSTANCE. SITE IS INDICATED AS BEING READY FOR INSEPCTION. IT WAS NOTED JUST RECENTLY THAT THE DRUG SUBSTANCE SITES, [redacted] (b) (4) WERE LISTED IN THE DRUG MASTER FILE [redacted] (b) (4) FOR THE DRUG SUBSTANCE [redacted] (b) (4). THES FIVE SITES ARE SUPPORTING SITES THAT PERFORM IMPORTANT TESTING FOR THE DRUG SUBSTANCE. HENCE THESE SITES ARE BEING LISTED IN EES. (on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-2007				PERIP
SUBMITTED TO DO	20-NOV-2007	PS			ADAMSS
ASSIGNED INSPECTION T	[redacted] (b) (4)	PS			ADAMSS
INSPECTION SCHEDULED	[redacted] (b) (4)		[redacted] (b) (4)		IRIVERA

UR Inspected. Report by OC 4/[illegible]

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blishment: [redacted] (b) (4)

DMF No: [redacted] (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS LAB PERFORMS IDENTIFICATION BY AMINO ACID ANALYSIS AND RESIDUAL ORGANIC SOLVENTS BY GC. (on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JAN-2008		[redacted] (b) (4)		PERIP
SUBMITTED TO DO	24-JAN-2008	GMP	[redacted] (b) (4)		ADAMSS
ASSIGNED INSPECTION T	[redacted] (b) (4)	GMP			ADAMSS

not yet scheduled as of 4/02

Establishment: [redacted] (b) (4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

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

Estab. Comment: SITE IS RESPONSIBLE FO THE FORMULATIION, (b) (4) , ASSEMBLY, PACKAGING, AND LABELING STERILITY AND ENDOTOXIN TESTING AND RELEASE OF DRUG PRODUCT. SITE IS READY FOR INSPECTION. (on 19-NOV-2007 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-2007				PERIP
SUBMITTED TO DO	20-NOV-2007	PS			ADAMSS
ASSIGNED INSPECTION T	(b) (4)	PS			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		ADAMSS
INSPECTION PERFORMED	(b) (4)		(b) (4)		ADAMSS
DO RECOMMENDATION	16-APR-2008			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
OC RECOMMENDATION	16-APR-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: (b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS LAB PERFORMS TESTING OF MICROBIAL LIMITS FOR THE DRUG SUBSTANCE

(on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	(b) (4)	GMP			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA

Inspection report UR by OC 4/03

blishment: (b) (4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS LAB PERFORMS IDENTIFICATION OF THE DRUG SUBSTANCE BY ELECTROSPRAY IONIZATIION-MASS SPECTROMETRY (ESI-MS) (on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP			ADAMSS
RECOMMENDATION	07-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

ile: CTL OAI Status: NONE

Estab. Comment: THIS SITE IS RESPONSIBLE FOR ALL OTEHR RELEASE TESTING. THE REGISTRATION NUMBER LISTED IN TEH NDA IS 3004908885 BUT COULD NOT BE

FOUND IN THE SYSTEM. SITE IS READY FOR INSPECTION. (on 19-NOV-2007 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-2007				PERIP
OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: [redacted] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

THIS SITE IS RESPONSIBLE FOR OSMOLALITY TESTING FOR RELEASE, STERILITY AND BACTERIAL ENDOTOXINS TESTING, AND PART OF STABILTY TESTING PROGRAM. SITE IS READY FOR INSEPCTION. (on 19-NOV-2007 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-2007				PERIP
OC RECOMMENDATION	20-NOV-2007			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: [redacted] (b) (4)

DMF No: [redacted] (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS LAB PERFORMS [redacted] (b) (4) TESTING BY INDUCTIVE COUPLED PLASMA EMISSION SPECTROSCOPY (ICP-OES)OF THE DRUG SUBSTANCE (on 22-JAN-2008 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	22-JAN-2008				PERIP
SUBMITTED TO DO	24-JAN-2008	GMP			ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS

OC RECOMMENDATION 07-MAR-2008 ACCEPTABLE ADAMSS

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/

NIKOO N MANOCHEHRI-KALANTARI
08/30/2011