

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125293

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 8/9/2010
To: Administrative File, STN 125293/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 8/10/10*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 8/10/10*
Subject: Review of a BLA amendment in response to a complete response letter
Applicant: Savient Pharmaceuticals, Inc.
US License: 1801
Facility: Bio-technology General Ltd (BTG), Kiryat Malachi, Israel
FEI: 3000164186
Enzon Pharmaceuticals, Inc., Indianapolis, IN
FEI: 1000517970
Product: Krystexxa™ (Pegloticase)
Dosage: 8 mg uricase/1 mL/vial, intravenous infusion
Indication: Treatment of intravenous infusion intended for patients with treatment failure
gout to control hyperuricemia and to manage the signs and symptoms of gout
PDUFA Date: 9/14/2010

Recommendation: BLA 125293, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

This is a resubmission to BLA STN125293 for Krystexxa for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout. This resubmission addresses the deficiencies listed in July 31, 2009 complete response letter. This review assesses Savient's response to eight CMC microbiology deficiency listed in the complete response letter.

(b) (4)

BLA STN125293/0/37, Savient, Pegloticase

Cc: WO51: Chi
WO51: Hughes
WO22: Sista
HFD-328, TFRB Blue Files (STN 125293)

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 7/21/2009
To: Administrative File, STN 125293/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 7/22/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 7/22/09*
Subject: Addendum to review memo for New Biologic License Application (BLA) STN 125293/0 dated 7/1/2009
Applicant: Savient Pharmaceuticals, Inc.
US License: 1801
Facility: Enzon Pharmaceuticals, Inc., Indianapolis, IN
FEI: 1000517970
Product: Krystexxa™ (Pegloticase)
Dosage: 8 mg uricase/1 mL/vial, intravenous infusion
Indication: Treatment of intravenous infusion intended for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout
PDUFA Date: August 1, 2009

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following post-marketing requirement:

The current selected small shipper did not meet the pre-determined temperature acceptance criterion for the maximum load at summer profile and winter profile, and the minimum load at winter profile during the validation runs. The applicant should develop and validate a shipper that is suitable to transport the finished product vials within the continental US. The worst-case conditions should be used in the shipper validation studies.

A separate evaluation of the Bio-Technology General (Israel) Ltd. (BTG), the drug substance manufacturing site and an alternate testing lab for release and stability testing of the drug product, will be conducted by the compliance officer at CDER/OC/DMPQ.

This review amends the drug product review memo for Savient's BLA STN125293/0 by Bo Chi dated 7/1/2009 with new information submitted by the applicant (eCTD sequence number 029, dated 7/9/2009) pertaining to the validation of the microbial challenge test for container closure integrity.

Satisfactory

Conclusion

The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following post-marketing requirement:

The current selected small shipper did not meet the pre-determined temperature acceptance criterion for the maximum load at summer profile and winter profile, and the minimum load at winter profile during the validation runs. The applicant should develop and validate a shipper that is suitable to transport the finished product vials within the continental US. The worst-case conditions should be used in the shipper validation studies.

Cc: WO51: Chi
WO51: Hughes
WO22: Walker
HFD-328, TFRB Blue Files (STN 125293)

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: 14 July 2009
To: Administrative File, STN 125293/0
From: Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *met 14 July 09*
Endorsement: Concepcion Cruz, Acting Branch Chief, CDER/OC/DMPQ/MAPCB **CB*
Kalavati Suvarna, Ph.D., Acting Team Leader, *14/7/09*
CDER/OC/DMPQ/MAPCB/BMT *7/15/09*
Subject: Addendum to review memo of 30 June 2009
US License: #1801
Applicant: Savient Pharmaceuticals, Inc.
Mfg Facility: Bio-Technology General (Israel) Ltd. (BTG); Kiryat Malachi, Israel
(FEI 3000164186)
Product: Krystexxa® (pegloticase)
Dosage: [to be determined]
Indication: treatment of intravenous infusion intended for patients with treatment failure
gout to control hyperuricemia and to manage the signs and symptoms of gout
Due Date: 30 July 2009

Recommendation for Approvability

The sponsor submitted an amendment (eCTD #0030) on 10 July 2009 to address bioburden limits, endotoxin limits, and hold times for intermediates. The information provided resolved some but not all of the deficiencies described in the earlier memo for drug substance by Mary Farbman on 30 June 2009. The BLA as amended is not recommended for approval.

Conclusions

STN 125293/0, as amended, was reviewed from a microbial control and microbiology product quality perspective. The list of deficiencies was modified to reflect the new information included in the amendment. The application is not recommended for approval.

Cc: WO Bldg 51, Farbman
WO Bldg 51, Suvarna
WO Bldg 51, Hughes
WO Bldg 51, Dillon
WO Bldg 51, Blue Files (STN 125293/0)
WO Bldg 22, Walker

List of Microbiology-Related Deficiencies for Pegloticase Drug Substance



(b) (4)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: 14 July 2009
To: Administrative File, STN 125293/0
From: Kalavati Suvarna, Ph.D., Acting Team Leader,
CDER/OC/DMPQ/MAPCB/BMT *KS 7/14/09*
Subject: Addendum to the Team Leader Review Memo of 02 July 2009
US License: #1801
Applicant: Savient Pharmaceuticals, Inc.
Mfg Facility: Bio-Technology General (Israel) Ltd. (BTG); Kiryat Malachi, Israel
(FEI 3000164186)
Product: Krystexxa® (pegloticase)
Dosage: [to be determined]
Indication: Treatment of intravenous infusion intended for patients with treatment failure
gout to control hyperuricemia and to manage the signs and symptoms of gout
Due Date: 30 July 2009

Recommendation for Approvability

STN 125293/0 is not recommended for approval from a microbial control and microbiology product quality perspective.

The team leader memo of 02 July 2009 is being amended here to reflect an addendum made to the original primary microbiology drug substance review dated 30 June 2009 by Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT. The addendum reflects the review of an amendment (eCTD#0030) submitted by the sponsor on 10 July 2009. The amendment did not fully address the deficiencies described in the 30 June 2009 review memo. There is no change in the recommendation for approvability. The application is not recommended for approval.

The Acting Team Leader concurs with the conclusions provided in the 14 July 2009 review memo addendum by Mary Farbman.

Cc: WO Bldg 51, Farbman
WO Bldg 51, Suvarna
WO Bldg 51, Hughes
WO Bldg 51, Dillon
WO Bldg 51, Blue Files (STN 125293/0)
WO Bldg 22, Walker



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 7/2/2009
To: Administrative File, STN 125293/0
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT
Endorsement: Concepcion Cruz, Acting Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: New Biologic License Application (BLA)
Applicant: Savient Pharmaceuticals, Inc.
US License: 1801
Facilities: Bio-Technology General (Israel) Ltd. (BTG), Kiryat Malachi 83104, Israel, FEI 3000164186
Enzon Pharmaceuticals, Inc., Indianapolis, IN, FEI: 1000517970
Product: Krystexxa™ (Pegloticase)
Dosage: 8 mg uricase/1 mL/vial, intravenous infusion
Indication: Treatment of intravenous infusion intended for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout
PDUFA Date: August 1, 2009

PPH
2/10/09
C/C 7/2/2009

Recommendation: The BLA 125293, as amended, is not recommended for approval at this time from a microbiology product quality perspective. The following issues were not resolved during the review period for this application:

(b) (4)

Drug Product (Section 3.2.P)

The results from a microbial challenge validation study (container closure integrity test) were not submitted at the time of this review. The firm is currently conducting the study and committed to provide the data by July 10th.

The following item is requested as a post-market requirement:

The current selected small shipper did not meet the pre-determined temperature acceptance criterion for the maximum load at summer profile and winter profile, and the minimum load at winter profile during the validation runs. The sponsor should develop and validate a shipper that is suitable to transport the finished product vials within the continental US. The worst-case conditions should be used in the shipper validation studies.

Establishment inspections and compliance with CGMPS:

A pre-license inspection of the contract manufacturer, Bio-Technology General (Israel) Ltd. (BTG), Be'er Tuvia Industrial Zone, Kiryat Malachi 83104, Israel, FEI 3000164186 was conducted on 6/3-10, 2009 and 13 FDA Form 483 observations were presented to the firm. BTG (Israel) manufactures the bulk drug substance for Savient. The inspection team recommended a non-concur BLA approval pending the implementation of corrective actions to resolve the CGMP deficiencies. The final decision will be made by the compliance officer at CDER/OC/DMPQ/ ICT once a response to the 483 observations is provided by the contract manufacturer.

The drug product is manufactured at Enzon Pharmaceuticals, Inc., 6925 Guion Rd, Indianapolis, IN 46268, FEI 1000517970. The site underwent a surveillance inspection on June 9-12, 2009 and was initially classified VAI a final district decision has not yet been made. The pre-approval inspection of this facility was waived (memo attached to the primary review for the drug product).

Conclusion

- I. The BLA 125293, as amended, is not recommended for approval from a product quality microbiology perspective. Deficiencies and post-marketing commitments that should be communicated to the sponsor are listed above.
- II. Information and data in this submission not related to microbiology product quality, including drug substance microbial control and drug product sterility assurance should be reviewed by an OBP reviewer(s).
- III. The pre-license inspection of the drug substance manufacturer and testing site, Bio-Technology General (Israel) Ltd. (BTG), was conducted on June 3-10, 2009 and a 13 item Form FDA 483 was presented to the firm. The initial recommendation by the inspection team was non-concur with the approval of the BLA. The BLA cannot be recommended for approval until the inspection outcome is finalized and the 483 items as are satisfactorily addressed. A final determination of the inspection outcome will be provided at a later date by compliance Officer in CDER/OC/DMPQ/ICT after the firm has addressed the 483 observations.

BLA STN125293/0, Savient, Pegloticase

The pre-approval inspection of the drug product manufacturer, Enzon, has been waived (see pre-approval inspection waiver memo attached to the primary drug product review).

Cc: WO51: Chi
WO51: Farbman
WO51: Hughes
WO22: Walker
HFD-328, TFRB Blue Files (STN 125293)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 7/1/2009
To: Administrative File, STN 125293/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 7/2/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 7/1/09*
Subject: New Biologic License Application (BLA)
Applicant: Savient Pharmaceuticals, Inc.
US License: 1801
Facility: Enzon Pharmaceuticals, Inc., Indianapolis, IN
FEI: 1000517970
Product: Krystexxa™ (Pegloticase)
Dosage: 8 mg uricase/1 mL/vial, intravenous infusion
Indication: Treatment of intravenous infusion intended for patients with treatment failure
gout to control hyperuricemia and to manage the signs and symptoms of gout
PDUFA Date: August 1, 2009

Recommendation: The approval of the drug product part of this application, as amended, is pending until the microbial challenge test (container closure integrity test) validation summary data is provided and reviewed. The firm is currently conducting the study and committed to provide the data by July 10th.

The following item will be reviewed as a post-market commitment: The current selected small shipper did not meet the pre-determined temperature acceptance criterion for the maximum load at summer profile and winter profile, and the minimum load at winter profile during the validation runs. Develop and validate a shipper that is suitable to transport the finished product vials within the continental US. The worst-case conditions should be used in the shipper validation studies.

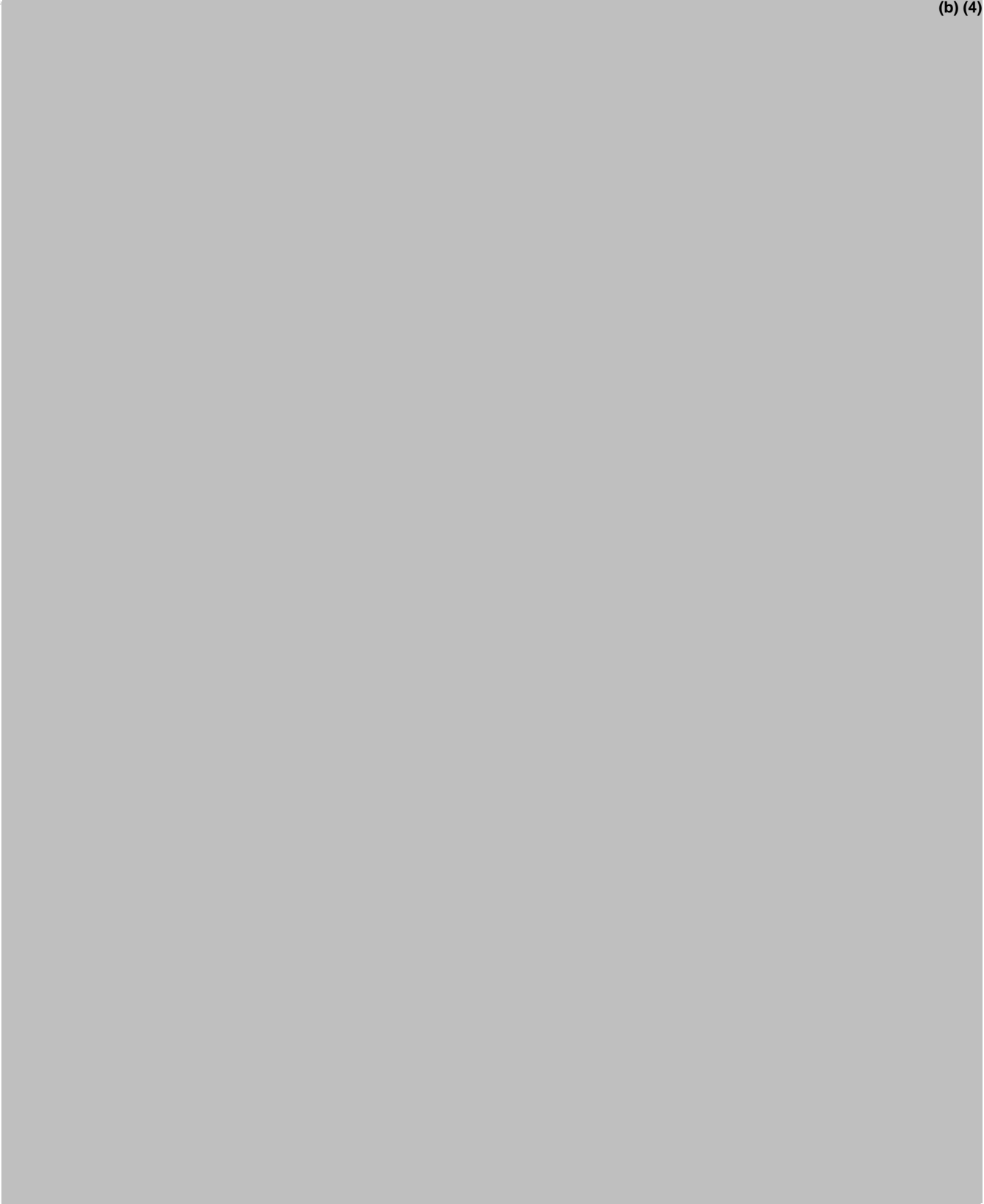
A separate evaluation of the Bio-Technology General (Israel) Ltd. (BTG), the drug substance manufacturing site and an alternate testing lab for release and stability testing of the drug product, will be conducted by the compliance officer at CDER/OC/DMPQ.

Review Summary

Savient Pharmaceuticals, Inc. has submitted this BLA for pegloticase to treat patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout. The drug substance is manufactured at Bio-Technology General Ltd. (BTG), Kiryat Malachi,

Israel. The drug product (DP) is manufactured at Enzon Pharmaceuticals, Inc., Indianapolis, IN. The application contains CMC information in an eCTD format.

(b) (4)



**30 Page(s) have been Withheld in Full
immediately following this page as B4
(CCI/TS)**

Enzon Pharmaceuticals, Inc.
6925 Guion Rd
Indianapolis, IN 46268
FEI 1000517970

Inspected June 9-12, 2009 and initially classified VAI. The SVS profile was covered; however a final district decision has not yet been made.

Bio-Technology General (Israel) Ltd. (BTG)
Be'er Tuvia Industrial Zone
Kiryat Malachi 83104
Israel
FEI 3000164186

Inspected 6/3/2009-6/10/2009 and initially classified as non-concur approval. The final decision will be made by the compliance officer at CDER/OC/DMPQ.

Conclusion

- I. The approval of the drug product part of this application, as amended, is pending until the microbial challenge test (container closure integrity test) validation summary data is provided and reviewed.

The following item will be reviewed as a post-market commitment: The current selected small shipper did not meet the pre-determined temperature acceptance criterion for the maximum load at summer profile and winter profile, and the minimum load at winter profile during the validation runs. Develop and validate a shipper that is suitable to transport the finished product vials within the continental US. The worst-case conditions should be used in the shipper validation studies.

- II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.
- III. The pre-approval inspection of the drug product manufacturer Enzon has been waived (see attached pre-approval inspection waiver memo).

A separate evaluation of the Bio-Technology General (Israel) Ltd. (BTG), the drug substance manufacturing site and an alternate testing lab for release and stability testing of drug product, will be conducted by the compliance officer at CDER/DMPQ.

Cc: WO51: Chi
WO51: Hughes
WO22: Walker
HFD-328, TFRB Blue Files (STN 125293)

List of microbiology product quality deficiencies

The approval of the drug product part of this application, as amended, is pending until the microbial challenge test (container closure integrity test) validation summary data is provided and reviewed. The firm is currently conducting the study and committed to provide the data by July 10th.



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: 30 June 2009
To: Administrative File, STN 125293/0
From: Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *mf 30 Jun 09*
Endorsement: Concepcion Cruz, Acting Branch Chief, CDER/OC/DMPQ/MAPCB *CPH 6/30/09*
Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *CPH 6/30/09*
Subject: New BLA
US License: #1801
Applicant: Savient Pharmaceuticals, Inc.
Mfg Facility: Bio-Technology General (Israel) Ltd. (BTG); Kiryat Malachi, Israel
(FEI 3000164186)
Product: Krystexxa® (pegloticase)
Dosage: [to be determined]
Indication: treatment of intravenous infusion intended for patients with treatment failure
gout to control hyperuricemia and to manage the signs and symptoms of gout
Due Date: 30 July 2009

Recommendation for Approvability

This BLA is not recommended for approval from a product quality/microbiology perspective. Furthermore, based on the outcome of a pre-license inspection of the pegloticase drug substance manufacturing facility, the inspectors have recommended a non-concur approval of the BLA. A list of deficiencies may be found on the last page of this memo.

Summary

Savient Pharmaceuticals, Inc., has submitted a BLA for its PEGylated uricase product Krystexxa® (pegloticase). The drug substance is manufactured at Bio-Technology General (BTG) in Kiryat Malachi, Israel. This review summarizes the Biotechnology Manufacturing Team's assessment of the microbial control over the drug substance manufacturing process. Our team's assessment of the sterility assurance of drug product will be provided in a separate review, written by Dr. Bo Chi.

Amendments in response to drug substance microbiology information requests were provided to the FDA on 03 April 2009 and 23 June 2009. These amendments helped to

address several of the problems with microbial control as described in the original BLA. However, multiple problems remain to be resolved. In particular:



A pre-license inspection of the Bio-Technology General (Israel) drug substance manufacturing facility occurred from June 3 to June 10, 2009 under FACTS Assignment No. 1065490. Drs. Patricia Hughes, Howard Anderson, and Mary Farbman participated in this inspection. The inspection resulted in a 13-item FDA Form 483 being given to the firm. As a result of the GMP deficiencies at the drug substance manufacturing firm, the inspection team recommends a non-concur approval of the BLA.

Because of the review deficiencies summarized above and the GMP deficiencies discovered on inspection, BMT recommends not approving the BLA.



Conclusions

- I. The BLA is not recommended for approval from a product quality/microbiology perspective. A list of deficiencies is attached to this memo.
- II. Information and data in the CMC portion of the BLA not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. A pre-approval inspection of BTG, the drug substance manufacturer, was conducted on 03-10 Jun 2009, and the Office of Compliance has not yet determined the compliance status of the firm resulting from that inspection.

Should the BLA be approved, a few minor follow-up inspectional issues should be addressed at the next surveillance inspection:

- The next surveillance inspection should review the shipping logs for pegloticase. The shipping validation for the minimum load was inadequately performed, and the firm has stated that only (b) (4) performed. The next surveillance inspection should ascertain whether any shipments of drug substance have been sent in any other configuration that has not been validated.
- Savient has committed to have BTG conduct follow-up studies for (b) (4) to ensure that the bioburden failures noted in report 06C1941-1 are in fact due to sampling errors rather than actual failures (b) (4). This data should be evaluated at the next surveillance inspection.

List of Microbiology-Related Deficiencies for Pegloticase Drug Substance



(b) (4)

Inspection Waiver Memorandum

Date: May 19, 2009
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT
To: BLA File – STN 125293/0
Subject: Recommendation to waive a pre-approval inspection at the drug product manufacturing facility
Sponsor: Savient Pharmaceuticals, Inc., U.S. License # 1801
Facility: Enzon Pharmaceuticals, Inc.
FEI: 1000517970
Product: Krystexxa™ (Pegloticase)
Dosage: 8 mg uricase/vial, intravenous infusion
Indication: For treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout
Through: Patricia Hughes, Ph.D., Team leader, *PH 5/19/09*
CDER/OC/DMPQ/MAPCB/BMT

Waiver Recommendation:

There are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at Enzon, IN. These processes were inspected last year with no significant regulatory findings. Concurrence is requested to waive the pre-approval inspection.

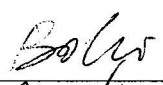
Clearance Routing

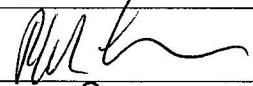
[Signature]
CONCUR / DO NOT CONCUR DATE 5/20/09

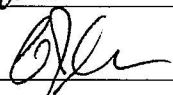
Rick Friedman, Director, Division of Manufacturing and Product Quality, Office of Compliance, CDER

Barry Cherry for A. Rosenberg
CONCUR / DO NOT CONCUR DATE 5-20-09
Amy Rosenberg, Director, Division of therapeutic proteins, Office of Biotechnology Products, Office of Pharmaceutical Science, CDER, HFD-123

Signed:

Bo Chi, WO, Building 51  DATE 5/19/09

Richard Ledwidge, HFD-123  DATE 5/20/09

Gibbes Johnson, HFD-123  DATE 5/20/09

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
☐ Drug Substance	Y	
☐ Drug Product	Y	
☐ Facilities and Equipment	Y	
☐ Adventitious Agents Safety Evaluation	Y	
☐ Novel Excipients	Y	
☐ Executed Batch Records	Y	
☐ Method Validation Package	Y	
☐ Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	
Drug Substance (API) [3.2.S]		
☐ general info	Y	
☐ nomenclature		
☐ structure (e.g. sequence, glycosylation sites)		
☐ properties		
☐ manufacturers	Y	
☐ facility name		
☐ full address (street, city, state, country)		
☐ is facility registered with FDA		
☐ FEI number		
☐ contact person	Y	Fax number not provided, but email has been fine thus far for communications with the sponsor.
☐ full name and title		
☐ telephone		
☐ fax		
☐ email		
☐ Confirmation by applicant that each API facility, including contractors and subcontractors, understand their specific role in the manufacturing process as described in the application.	N	Not provided. But the conformance lots have been made using the facilities.
☐ Confirmation by written statement from each API facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.)	Y	The firm has provided the manufacturing schedule for the drug substance site, where a PAI will be conducted.
	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
☐ API processing product type: primary mode of deriving API ☐ fermentation, bacterial host ☐ fermentation, mammalian host ☐ chemical synthesis ☐ extraction/isolation, only ☐ batch numbering and pooling scheme ☐ cell culture and harvest ☐ purification ☐ filling, storage and shipping	Y	
☐ description of manufacturing process ☐ batch numbering and pooling scheme ☐ cell culture and harvest ☐ purification ☐ filling, storage and shipping	Y	
☐ control of materials ☐ raw materials and reagents ☐ biological source and starting materials ☐ cell substrate: source, history, and generation ☐ cell banking system, characterization, and testing	Y	
☐ control of critical steps and intermediates ☐ justification of specifications ☐ analytical method validation ☐ reference standards ☐ stability	N	Justification of in-process limits for intermediates does not appear to be present. This issue is not critical for bioburden and endotoxin in-process limits. We will address this issue on review.
☐ process validation (prospective plan, results, analysis, and conclusions)	Y	
☐ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
☐ characterization of drug substance	Y	
☐ control of drug substance ☐ specification ☐ justification of specs. ☐ analytical procedures ☐ analytical method validation ☐ batch analyses ☐ consistency (3 consecutive lots)	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ justification of specs. ☐ reference standards ☐ container closure system ☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ○ protocol ○ results ○ method validation	Y Y Y	
Drug Product [3.2.P] ☐ description and composition ☐ pharmaceutical development ☐ manufacturers ○ facility name ○ full address (street, city, state, country) ○ is facility registered with FDA ○ FEI number ☐ contact person ○ full name and title ○ telephone ○ fax ○ email ☐ Confirmation by the applicant that each facility, including contractors and subcontractors, understands their specific role in the manufacturing process as described in the application. ☐ Confirmation by written statement from each facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.) ☐ batch formula ☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ☐ finished drug processing: ○ mixing/homogenizing components ○ dry powder mixing	Y Y Y Y N Y Y Y N	Not provided. But the conformance lots have been made using the facilities. The firm has provided the manufacturing schedule for the drug substance site, where a PAI will be conducted. This is not applicable.

CTD Module 3 Contents	Present?	If not, justification, action & status
○ granulation, wet ○ granulation, dry ○ granulation high/low shear ○ micro fluidization ○ emulsification ○ milling/micronization ○ sieving/particle sizing ○ spray drying ○ fluidized bed drying ○ tray drying ○ mixing, suspension ○ mixing, liquids not solution/suspension □ finished drug processing: forming dosing/delivery unit ○ compression (compaction of a powder, slug, or granules by a press; includes multilayer tablets prepared by more than one compression cycle.) ○ molding (Forming a solid dosage other than by compaction, as in making suppository, lozenge, pill, soap, softgel, and gum.) ○ fabrication, inhalers liquid and gas cold fill ○ fabrication, inhalers dry powder ○ fabrication, transdermals ○ fabrication, pre-filled syringe ○ filling, powder/granule ○ extrusion (other than as used in granulation) ○ coating, color/taste only ○ coating delay/extend ○ release rate (includes coating tablets as well as granules, beads, or pellets) ○ filling, solution ○ filling suspension ○ filling, liquids not solution/suspension ○ filling, semi-solid □ component and finished drug processing aseptic fill and sterilization ○ aseptic filling, manual process (including liquid and solid filling)	Y N Y	This is not applicable.

CTD Module 3 Contents	Present?	If not, justification, action & status
☐ aseptic filling, isolator process (enclosed environments for filling sterile drug, including blow-fill-seal, into which human intervention is not ○ expected or intended during process) ○ terminal sterilization (by any method, including steam, gas, dry heat, water, and radiation)	Y N	This is not applicable.
☐ other operations ○ lyophilization ○ irradiation by cyclotron (positron emission tomography (PET) drugs) ○ irradiation other (not intended to achieve sterility and not CYC) ○ not elsewhere classified (to be used infrequently and cautiously)	Y N	This is not applicable.
☐ finished drug processing: medical gas ○ gas separation (includes separation operations that also fill into vessels) ○ gas filling only	Y N	This is not applicable.
☐ controls of critical steps and intermediates	Y	
☐ process validation including aseptic processing & sterility assurance: ○ 3 <u>consecutive</u> lots ○ other needed validation data	Y	
☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
☐ control of drug product (justification of specifications; analytical method validation)	Y	
☐ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s)	Y	
☐ stability ○ summary	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Other components to be marketed (full description and supporting data, as listed above): ☐ other devices ☐ other marketed chemicals (e.g. part of kit)	 Y N Y N	Not applicable.
Laboratory (Contractor) ☐ laboratories ○ facility name ○ full address (street, city, state, country) ○ FEI number ☐ contact person ○ full name and title ○ telephone ○ Fax ○ email ☐ Confirmation by applicant that each test facility, including contractors and subcontractors, understands their specific role in the testing process as described in the application. ☐ Confirmation by written statement from each testing facility that they are ready for inspection, or the applicant identifies at what date the facility will be ready for inspection *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.) ☐ Each testing facility identified in the application and identification of the type of testing performed by the facility (if more than one type of testing is performed by a single facility, identify each type of testing.) ○ finished dosage ○ API ○ QC released testing/stability finished dosage or both ○ chemistry ○ microbiological Appendices for Biotech Products [3.2.A] ☐ facilities and equipment ○ manufacturing flow; adjacent areas	 Y Y Y N Y N Y	 See the answer above to the same question. See the answer above to the same question.

CTD Module 3 Contents	Present?	If not, justification, action & status
○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination □ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production □ novel excipients	Y N	This should be determined by the OBP reviewer.
USA Regional Information [3.2.R]		
□ executed batch records □ method validation package □ comparability protocols	Y Y Y	The information is provided in other sections.
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?		
□ legible □ English (or translated into English) □ compatible file formats □ navigable hyper-links □ interpretable data tabulations (line listings) & graphical displays □ summary reports reference the location of individual data and records □ all electronic submission components usable	Y Y Y Y Y Y	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
(including pilot facilities) using the final production process(es)?		
includes data demonstrating consistency of manufacture	Y	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	This should be assessed by the OBP reviewer.
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	This should be assessed by the OBP reviewer.
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	This should be assessed by the OBP reviewer.
certification that all facilities are ready for inspection	Y N	See answer to similar questions above.
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	This should be assessed by the OBP reviewer.
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	Y N Y Y N Y	This should be assessed by the OBP reviewer.
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	This should be assessed by the OBP reviewer.
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	
if this is a supplement for post-approval	Y N	Not applicable

Examples of Filing Issues	Yes?	If not, justification, action & status
manufacturing changes, is animal or clinical data needed? Was it submitted?		

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): File

For Applications: Were any potential review issues identified for the day 74 letter? No

Reviewer: Mary E. Farberman 15 Dec 08
Bollin 12/15/08 Type (circle one): Product (Chair) Facility (DMPQ)
 (signature/ date)

Concurrence:
 Branch/Lab Chief: [Signature] 12/15/08 Division Director: _____
 (signature/ date) (signature/ date)