CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022200Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

01-NOV-2011

NDA: 22-200/N-000 (Class 2 Re-submission)

Drug Product Name
Proprietary: BYDUREON™
Non-proprietary: exenatide for injectable suspension

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
28-JUL-2011	28-JUL-2011	28-JUL-2011	08-AUG-2011

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
22-APR-2010 04-MAY-2009	2	22-JUL-2010
01-SEP-2009 20-NOV-2009	1	01-MAR-2010

Applicant/Sponsor
Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive,
San Diego, CA 92121-3030
Representative: Orville Kolterman, MD
Sr. VP Research & Development
Telephone: (858) 642-7153

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology recommends APPROVE.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Class 2 NDA Resubmission following a second Complete Response.

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE:

Drug Substance (API): (3 sites)

Lonza Braine, S.A.
Chaussée de Tubize 297
B – 1420 Braine-l'Alleud
Belgium

Mallinckrodt Tyco Health, Inc.
3600 North Second Street
St. Louis, MO 63147

(b) (4)

Drug Product:
Amylin Ohio, LLC
8814 Trade Port Drive
West Chester, OH 45071

Drug Product Diluent:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Powder for subcutaneous injection.
- Extended release suspension.
- 2mg per dose.

5. METHOD(S) OF STERILIZATION:

Drug Product: (b) (4) Processing
Diluent: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Glycemic control

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS:

1) The subject submission was submitted electronically in CTD format. It is recorded as Supporting Document 43 in DARRTS and as Amendment 0034 in the EDR. The EDR Amendment number is out of sequence with respect to the submission date. The Resubmission addresses deficiencies in the Agency's CR letter dated 18-OCT-2010. The latter represented a second CR. A first CR was issued 12-MAR-2010.

2) In a second microbiology quality review dated 22-JUL-2011 the Reviewer recommended NDA approval. The second CR dated 18-OCT-2010 was issued for reasons unrelated to microbiology quality. The current review considers stability data and proposed retest or expiry periods for the drug substance, drug product, and diluent that were included in a 28-JUL-2011 Resubmission Response to the 18-OCT-2010 CR. The information has no relevance to the deficiencies upon which the second CR was based, but the Applicant proposed to include it in the Resubmission in a meeting request dated 02-JUN-2011. This request was granted in an Agency response dated 06-JUN-2011.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval from a microbiology quality standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product consists of a sterile drug product microsphere powder formulation in a vial and a sterile diluent in a syringe. The drug product is intended for suspension using a sterile diluent. All of the solutions, (b) (4) vessels and equipment. The entire manufacturing process for the drug product suspension is a (b) (4) Drug product is filled and stoppered (b) (4) The sterile diluent is manufactured at a second location and (b) (4) The sterile diluent syringes are shipped to the drug product manufacturer for final packaging with the drug product.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Steven Fong, Ph. D.
Microbiology Reviewer

B. Endorsement Block _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

CC: NDA 22-200

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/s/

STEVEN E FONG
11/01/2011
Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE
11/01/2011
I concur.

Product Quality Microbiology Review

20 July 2010

NDA: 22-200/N-000 (Class 2 Re-submission)

Drug Product Name
Proprietary: BYDUREON™
Non-proprietary: exenatide for injectable suspension

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
22 APRIL 2010	22 APRIL 2010	22 APRIL 2010	23 APRIL 2010

Submission History (for amendments only):

Submit Date(s)	Microbiology Review #	Review Date(s)
04 MAY 2009 01 SEPT 2009 20 NOV 2009	**1**	26 FEBRUARY 2010

Applicant/Sponsor
Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive,
San Diego, CA 92121-3030
Representative: Orville Kolterman, MD
Sr. VP Research & Development
Telephone: (858) 642-7153

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from a microbiology product quality perspective.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Class 2 NDA Resubmission following Complete Response

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE:

Drug Substance (API): (3 sites)

Lonza Braine, S.A.
Chaussée de Tubize 297
B – 1420 Braine-l'Alleud
Belgium

Mallinckrodt Tyco Health, Inc.
3600 North Second Street
St. Louis, MO 63147

(b) (4)

Drug Product:
Amylin Ohio, LLC
8814 Trade Port Drive
West Chester, OH 45071

Drug Product Diluent:
(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Injection, powder, for suspension, extended release; subcutaneous; 2mg.

5. METHOD(S) OF STERILIZATION:

Drug Product: (b) (4) Processing
Diluent: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Glycemic control

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS:

- The submission is electronic in eCTD format. It is recorded as Supporting Document 23 in DARRTS. It is a re-submission to address the deficiencies in the Agency's Complete Response letter dated 12 March 2010.
- A T-con was held with the Applicant on 08 April 2010 to discuss the microbiology deficiencies (specifically Deficiency #1.i.) in the CR letter. Background information was supplied by the Applicant prior to that T-con.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product consists of a sterile drug product microsphere powder formulation in a vial and a sterile diluent in a syringe. The drug product is intended for suspension using a sterile diluent. All of the solutions, (b) (4) (b) (4) vessels and equipment. The entire manufacturing process for the drug product suspension is a (b) (4) operations. Drug product is filled and stoppered (b) (4) The sterile diluent is manufactured at a second location and is (b) (4) The sterile diluent syringes are shipped to the drug product manufacturer for final packaging with the drug product.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Robert J. Mello, Ph. D.
Senior Microbiology Reviewer

B. Endorsement Block _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

CC: NDA 22-200

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

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/s/

ROBERT J MELLO
07/21/2010

JOHN W METCALFE
07/22/2010
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-200	**Applicant: Amylin Pharmaceuticals, Inc**	**Submit Date: 22 APRIL 2010**
Drug Name: Bydureon™ (exenatide extended-release for injectable suspension)	**NDA Type: 505 (b)(1) (Class 1 Re-submission)**	**Received Date: 22 APRIL 2010**

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		
9	Is this NDA fileable? If not, then describe why.	X		**Submission is Fileable**

Additional Comments: This is a CLASS 1 Complete Response Resubmission of NDA 22-200 submitted in eCTD format accessible through the EDR/Global Submit Review system. The applicant has included responses to the microbiology product quality deficiencies listed in the Agency's Complete Response letter dated 12 MARCH 2010. The submission is fileable.

Robert J. Mello, Ph.D. Date
Reviewing Microbiologist

John W. Metcalfe, Ph. D. Date
Microbiology Secondary Reviewer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

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/s/

ROBERT J MELLO
04/29/2010

JOHN W METCALFE
04/29/2010
I concur.

Product Quality Microbiology Review

26 FEBRUARY 2010

NDA: 22-200/N-000

Drug Product Name
Proprietary: BYDUREON™
Non-proprietary: exenatide for injectable suspension

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04 MAY 2009	05 MAY 2009	14 MAY 2009	15 MAY 2009
01 SEPT 2009	01 SEPT 2009	n/a	n/a
20 NOV 2009	20 NOV 2009	n/a	n/a

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive,
San Diego, CA 92121-3030
Representative: Dawn Viveash, MD
VP Regulatory Affairs and Safety
Telephone: (858) 309-7658

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is approvable pending receipt and review of additional information. (See review Section 3)

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE:

1) Drug Substance (API):

- Lonza Braine, S.A.
  Chaussée de Tubize 297
  B – 1420 Braine-l'Alleud
  Belgium

- Mallinckrodt Tyco Health, Inc.
  3600 North Second Street
  St. Louis, MO 63147

(b) (4)

2) Drug Product:

- Amylin Ohio, LLC
  8814 Trade Port Drive
  West Chester, OH 45071

- Drug Product Diluent:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Injection, powder, for suspension, extended release; subcutaneous; 2mg.

5. METHOD(S) OF STERILIZATION:

Drug Product: (b) (4) Processing

Diluent: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Glycemic control

B. SUPPORTING/RELATED DOCUMENTS:

- Letter of Authorization to reference DMF [redacted] (b) (4)
- Microbiology Review of DMF [redacted] (b) (4)

C. REMARKS:

- An Initial Quality Assessment was filed in DARRTS on 6 June 2009. A consult was submitted requesting review of (1) the microbiology controls for the drug substance and drug product, and (2) the sterilization and [redacted] (b) (4) processing validation for the drug product and diluent.
- The submission is electronic in eCTD format.
- The September 1, 2009 amendment contained updated information on bacterial endotoxin and sterility testing.
- The November 20, 2009 amendment contained updated data on container/closure integrity testing to support a [redacted] (b) (4) holding period for bulk microspheres storage prior to [redacted] (b) (4).
- The drug product microspheres are referred to as exenatide QW (QW = once per week) throughout the submission.

filename: N022200N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending receipt and review of additional information.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product consists of a sterile drug product microsphere powder formulation in a vial and a sterile diluent in a syringe. The drug product is intended for suspension using a sterile diluent. All of the solutions, (b) (4) vessels and equipment. The entire manufacturing (b) (4) process for the drug product suspension is a (b) (4) operations. Drug product is filled and stoppered (b) (4) The sterile diluent is manufactured at a second location and (b) (4) The sterile diluent syringes are shipped to the drug product manufacturer for final packaging with the drug product.

B. Brief Description of Microbiology Deficiencies –

- (b) (4)
-
-

C. Assessment of Risk Due to Microbiology Deficiencies – The deficiencies negatively impact (b) (4) of the drug product microsphere vials. Distribution (b) (4) could result.

III. Administrative

A. Reviewer's Signature _____

Robert J. Mello, Ph. D.
Microbiology Reviewer

B. Endorsement Block _____

Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

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/s/

ROBERT J MELLO
03/01/2010

STEPHEN E LANGILLE
03/01/2010

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-200 **Applicant: Amylin Pharmaceuticals, Inc.** **Letter Date: 04 MAY 2009**

Drug Name: BYDUREON™ exenatide for injectable suspension **NDA Type: 505 (b)(1)** **Stamp Date: 05 MAY 2009**

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	**X**		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	**X**		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	**X**		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		**X**	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity (CCI) studies?	**X,** (CCI)		Product is packaged for single use and is not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	**X**		
7	Has the applicant submitted the results of analytical method verification studies?		**X**	See comment below
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	N/A
9	Is this NDA fileable? If not, then describe why.	**X**		

Additional Comments: BET and sterility methods were cited as USP<85> and USP<71>, respectively. Actual test methods and their associated validation reports were not provided. The applicant should provide copies of the current test procedures for bacterial endotoxin and sterility testing of the drug product used at release and during stability. Also, the applicant should submit copies of the BET and sterility assay validation reports (REST080763 and REST080762, respectively).

Robert J. Mello, Ph.D. Reviewing Microbiologist Date

James McVey, Microbiology Team Leader Date

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/s/

Robert Mello
6/15/2009 12:55:10 PM
MICROBIOLOGIST

NDA is fileable

James McVey
6/15/2009 01:15:22 PM
MICROBIOLOGIST
I concur.