CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210605Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval
(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 210605
Review 3
Review Date: 5/22/2020

Drug Name/Dosage Form	Insulin glargine injection/ Solution for injection
Trade Name	Semglee
Strength	100 units/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Mylan Pharmaceuticals Inc..

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission and Amendments	*12/16/2019, 3/09/2020, 3/11/2020, 4/16/2020, and 5/12/2020*	*Quality (Module 3.2. and 1.1)*

Quality Review Team

DISCIPLINE	REVIEWER (Original)	REVIEWER (Resubmission 1)	REVIEWER (Resubmission 2)	DIVISION
Drug Substance	Joseph Leginus	Joseph Leginus	-	ONDP
Drug Product	Muthukumar Ramaswamy	Muthukumar Ramaswamy	-	ONDP
Process	Joanne Wang	-	-	OPMA
Microbiology	Jennifer Patro	Jennifer Patro	-	OPMA
Process/Facility	Vidya Pai	Vidya Pai	Vidya Pai	OPMA
Regulatory Business Process Manager	Anika Lalmansingh	Leeza Rahimi	Leeza Rahimi	OPRO
Application Technical Lead	Muthukumar Ramaswamy	Muthukumar Ramaswamy	Muthukumar Ramaswamy	ONDP
Facility (CDRH)	Habacuc Barrera	Rong Guo	-	CDRH

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs: (b) (4)

A. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105279	Insulin Glargine Injection

2. CONSULTS None

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommendation for NDA 210605 is approval. This recommendation includes acceptable recommendation from the Office of Pharmaceutical Manufacturing Assessment (OPMA) for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

NDA 210605 is a 505(b)(2) application for Semglee (insulin glargine injection) 100U/mL with Lantus (insulin glargine injection) 100U/mL as the referenced product. The proposed product is a clear, colorless solution filled in 10mL vial or in 3mL prefilled pen and is intended for subcutaneous injection. With the exception of polysorbate 20 content, the vial and pen presentations have the same product composition and strength. Mylan assigned code for insulin glargine is MYL-1501D. The product is intended for glycemic control in adults and children with diabetes. For maximum daily dose information, please refer to CDTL's memo.

B. Quality Assessment Overview

The original NDA submission for Semglee (insulin glargine injection) was submitted on 4/27/2017. The OPQ recommendation for the original submission was complete response (CR) due to manufacturing facility related issues identified during pre-approval inspection at Biocon Sdn. Bhd., Malaysia (FEI #3011248248) and microbiology issues identified during NDA review. The CMC recommendation from drug substance, drug product, and process reviewers for the original submission was for approval. For more details, please refer to OPQ integrated quality review for NDA 210605 dated 4/5/2018 in Panorama.

On Feb 28, 2019, Mylan resubmitted the NDA application with relevant CMC information necessary to address the microbiology deficiencies outlined in the CR letter. The CR response letter indicated that Biocon Sdn., Bhd., Malaysia has implemented corrective actions (CAPAs) and the manufacturing site is ready for inspection. The resubmission also identified Biocon Sdn., Bhd., as additional site for pre-filled pen assembly, packaging, and testing of finished product process validation data to support the same. Dr. Jennifer Patro reviewed the applicant's response to microbiology related deficiencies and concluded that the response was adequate to support the NDA application. FDA re- inspected the drug substance, drug product, and finished product manufacturing facility (Biocon Sdn. Bhd., Malaysia, FEI #3011248248) between June 24, 2019 – July 5th , 2019. The re- inspection resulted in the issuance of a 12-item Form FDA 483 due to the facility's lack of readiness for manufacturing and data integrity concerns. The OPQ recommendation for the Feb. 2019 resubmission was complete response (CR). For more details, please refer to OPQ integrated quality review for NDA 210605 dated 8/22/2019 in Panorama

On December 16, 2019, Mylan resubmitted the NDA application with quality response to comments outlined in the CR letter and indicated that manufacturing site at Biocon Sdn., Bhd., Malaysia is ready for inspection. The CR response letter indicated that Biocon Sdn., Bhd., has implemented corrective actions (CAPAs) to address FDA's concern. FDA re- inspected the Biocon Sdn. Bhd. manufacturing facility located in Malaysia (FEI #3011248248) between 2/10/

2020 to 2/21/ 2020. The follow-up inspection was focused on reviewing firm's implementation of corrective actions and establishing the effectiveness as well as assessment of overall quality systems at facility to support the manufacturing/testing operations. The facility reinspection resulted in a 3-item FDA 483. The initial field recommendation was VAI – with recommendation to approve the application.

Dr. Pai reviewed the facility information associated with this application including the applicant's response to recent FDA 483 observations. Her overall recommendation for facilities associated with this NDA is approval. For additional details, please refer to the facility review dated 5/21/20 in Panorama under NDA 210605 resubmission.

Per facility review, post approval inspections are recommended for the following sites:

1. (b) (4) (Laboratory coverage, CTL/LBI)
2. Biocon Limited, Bangalore India, FEI#3003981475 (Device Coverage, IDD).
3. Mylan GmbH, Thurauerstrasse 40, Zurich, Switzerland, CH-8050, FEI#3007160792 (Device Coverage, IDD).

Based on available stability data, a shelf-life of 24 months is granted for the finished product in cartridge/prefilled pen and vials when stored at 5°C ± 3°C and 28 day in-use period for storage at up to 30°C.

OVERALL ASSESSMENT AND SIGNATURE:

From CMC perspective, the NDA 210605 is recommended for approval.

Muthukumar Ramaswamy, Ph.D. 5/22/20

Application Technical Lead Name and Date

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Muthukumar Ramaswamy

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Recommendation: Complete Response

(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 210605
Review 2
Review Date: 8/22/19

Drug Name/Dosage Form	Insulin glargine injection/Solution for injection
Trade Name	Semglee
Strength	100 units/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Mylan LLC.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission and Amendments	*2/28/19, 3/07/19, 5/06/19, 5/24/19, 6/13/19, 6/27/19, and 7/11/19*	*Quality (Module 3.2. and 1.1)*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Division of New Drug API/ONDP
Drug Product	Muthukumar Ramaswamy	New Drug Products II/ONDP
Microbiology	Jennifer Patro	Microbiology Assessment/OPF
Process /Facility (OPF)	Vidya Pai	Division of Inspectional Assessment/OPF
Regulatory Business Process Manager	Leeza Rahimi	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products II/ONDP
Facility (CDRH)	Rong Guo	CDRH Compliance

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information in the NDA	LOA 1/24/17
	Type III				LOA 11/20/2013
	Type III				1/23/2017
	Type III				1/23/2017
	Type III			Adequate. Refer to microbiology review	1/23/2017
	Type V			Adequate. Refer to microbiology review	LOA 1/23/2017
	Type V				LOA 1/23/17
	Type II			Sufficient information in the NDA	LOA dated 4/26/2017

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105279 and amendments dated 10/22/2012 (Type C meeting), 4/4/2014 (EOP2 meeting), 2/24/2016 (Type C meeting), and 4/7/2016 (Advice/Information request)	Insulin Glargine Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 7/30/19 and 5/28/19	5/28/19 and 7/30/19	Rong Guo

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality for NDA 210605 resubmission is complete response due to issues related to drug substance and drug product manufacturing facility, Biocon Sdn. Bhd., Johor, Malaysia (FEI # 3011248248).

FDA's pre-approval inspection of the drug substance and drug product manufacturing facility, Biocon Sdn. Bhd., Johor, Malaysia (FEI #3011248248) between June 24, 2019 – July 5th, 2019 resulted in a withhold recommendation due to objectionable conditions observed at the commercial manufacturing facility. To correct these deficiencies, the Firm has committed to completing several corrective actions and Quality Management System (QMS) improvement initiatives as outlined in the Process/Facility review. Successful completion and implementation of corrective actions and QMS improvements is required, before the facility can be considered as acceptable to support the NDA.

II. Summary of Quality Assessments

A. Product Overview

NDA 210605 is a 505(b)(2) application for Semglee (insulin glargine injection) 100U/mL with Lantus (insulin glargine injection) 100U/mL as the referenced product. The proposed product is a clear, colorless solution filled in 10mL vial or in 3mL prefilled pen and intended for subcutaneous injection. With the exception of polysorbate 20 content, the vial and pen presentations have the same product composition and strength. Mylan assigned code for insulin glargine is MYL-1501D.

B. Quality Assessment Overview

The CMC recommendation for the original NDA submission was complete response (CR) due to manufacturing facility related issues identified during pre-approval inspection at Biocon Sdn. Bhd. between Feb.6th -15th 2018 and microbiology issues identified during NDA review. The complete response letter issued for the original NDA submission contained additional CMC comments requiring the applicant to provide impurity profile comparison between Lantus and Semglee injection using Mylan in-house and USP insulin glargine monograph test methods and potency comparison between Lantus and Semglee injection. The CMC recommendation from drug substance, drug product, and process reviewers for the original submission was for approval. For more details, please refer to OPQ integrated quality review for NDA 210605 dated 4/5/2018 in Panorama.

On Feb 28, 2019, Mylan resubmitted the NDA application with relevant CMC information necessary to address the deficiencies outlined in the CR letter. The CR letter indicated that Biocon Sdn., Bhd., Malaysia has implemented 40 corrective actions (CAPAs) based on previous commitment to FDA and the manufacturing site is ready for inspection.

Mylan also provided the following CMC updates to the drug substance portion of the application: a) revision of an in-process control limit for an impurity, b) calculation of impurity levels using HPLC and SEC methods, and c) additional stability data.

Dr. Joseph Leginus has reviewed the CMC updates for drug substance (DS) and concluded that the drug substance information provided in the NDA is adequate to support the NDA. Based on available stability information, a retest period of (b) (4) was granted for the drug substance, (b) (4) (b) (4). For additional details, please refer to Dr. Leginus's review in Panorama under NDA 210605 resubmission dated 4/9/2019.

Dr. Jennifer Patro reviewed the applicant's response to microbiology related deficiencies and concluded that the response is adequate to support the NDA application. Please refer to Dr. Patro's review in Panorama under NDA 210605 resubmission dated 3/19/2019.

Per agency request, the applicant provided potency comparison between Lantus and Semglee drug product batches stored under accelerated storage conditions and end of expiry impurity profile comparison for Semglee and Lantus drug product batches using the USP insulin glargine injection monograph and Mylan in-house RP HPLC methods. Dr. Ramaswamy reviewed the response. His review concluded that Mylan batches had comparable potency to Lantus batches and the degradation rates for total impurities are comparable between two products.

The drug product review concluded that Mylan's in-house method is efficient at resolving (b) (4) glycosylated impurities, and deamidation products that elute close to the insulin glargine peak, while the USP method is able to separate late eluting peaks better (b) (4) (b) (4). Major individual impurities present in the MYL-1501 D drug product and Lantus are generally the same. Under accelerated storage conditions, the Lantus batches contained (b) (4) (b) (4). These impurities were not seen in Mylan batches. This is likely due to differences in DS manufacturing process. Drug product review concluded that no further impurity profile comparison between Lantus and Mylan using in-house and USP method is needed.

The original submission identified Biocon Limited, Bangalore India, (FEI#3003981475) as pre-filled pen assembly manufacturing site. The resubmission identified Biocon Sdn., Bhd., as additional site for pre-filled pen assembly, packaging, and testing of finished product. The applicant provided process validation and 3mo. of functional stability data for 3 batches to support the pre-filled pen assembly, packaging, and testing at Biocon Sdn., Bhd. Manufacturing process related information provided in the resubmission was reviewed by Dr. Pai. Process review concluded that the process information provided in the NDA resubmission is adequate. Please refer to Dr. Pai's review in Panorama under NDA 210605 resubmission dated 8/22/2019.

Mylan committed to submit end of expiry in-use stability data for the pre-filled pen assembled batches at L2 (i.e., 24 months at 5°C ± 3°C followed by 28 - 31 days at 30°C ± 2°C) tentatively by 1st Quarter, 2021. The NDA resubmission also contains updated stability information for commercial scale Process VI drug product batches filled in 3mL cartridges and filled in vials. Based on available stability data, a shelf-life of 24 months is granted for the cartridge/prefilled pen presentations and vials when stored at 5°C ± 3°C and 28 day in-use period for storage at up to 30°C. Drug product reviewer concluded that CMC information provided in the resubmission is adequate to support the NDA. Please refer to Dr. Ramaswamy's review in Panorama under NDA 210605 resubmission dated 7/29/2019.

Dr. Pai reviewed the facility compliance information for drug product and drug substance and finished product manufacturing facilities and provided the facility recommendation for the resubmission. FDA re- inspected the drug substance, drug product, and finished product manufacturing facility (Biocon Sdn. Bhd., Malaysia, FEI #3011248248) between June 24, 2019 –

July 5th , 2019. The re-inspection focused on (b) (4) manufacturing operations, (b) (4) (b) (4) and analytical data integrity with emphasis was on effectiveness of corrective actions implemented at the facility in response to the FDA's previous inspection findings. The inspection also covered medical device manufacturing operation including Management Controls, Design Controls, CAPA, and Production and Process Controls including procedures and related records.

FDA's re- inspection resulted in the issuance of a 12-item Form FDA 483, A withhold recommendation was issued for NDA-210605 due to the facility's lack of readiness for manufacturing and data integrity concerns.

To correct these deficiencies, the Firm has committed to completing several corrective actions (b) (4) (b) (4). Dr. Pai reviewed the corresponding establishment inspection report (EIR), the Firm's responses to each of the Form 483 observations and the timeline for the implementation of corrective actions and (b) (4) improvements. Her review concluded that the deficiencies identified during inspection cumulatively point to lack of complete manufacturing and control instructions and do not demonstrate that product can be reliably manufactured at commercial scale. Dr. Pai's review concluded that the applicant's proposed actions and commitments remain pending as of the date of this review.

Successful completion and implementation of corrective actions and (b) (4) improvements is required, before the facility can be considered as acceptable to support the NDA. Per facility review, post approval inspections are recommended for the following sites:

1. (b) (4) (Laboratory coverage, CTL/LBI)
2. Biocon Limited, Bangalore India, FEI#3003981475 (Device Coverage, IDD).
3. Mylan Gmbh, Thurauerstrasse 40, Zurich, Switzerland, CH-8050, FEI#3007160792 (Device Coverage, IDD).

Please refer to the facility review dated 8/22/19 in Panorama NDA 210605 resubmission for details.

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the NDA 210605 is <u>not</u> recommended for approval.

Muthukumar Ramaswamy, Ph.D. 8/23/19

Application Technical Lead Name and Date

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MICROBIOLOGY

Product Background:

NDA/ANDA: NDA 210605

Drug Product Name / Strength: MYL-1501D (Insulin Glargine) 100 U/mL SEMGLEE

Route of Administration: intramuscular injection

Applicant Name: Mylan

Manufacturing Site: Biocon Sd. Bhd. (930330-U)
No. 1, Jalan Bioteknologi 1,
Kawasan Perindustrian SiLC,
79200 Iskandar Puteri, Johor, Malaysia

Method of Sterilization: (b) (4)

Review Recommendation: **Recommended**

Review Summary: This is a sterile solution filled into 10 mL vials or 3 mL cartridges (pre-filled pens). (b) (4)

(b) (4)

List Submissions Being Reviewed: 05/11/18 CR Response; 02/28/19 CR Response

Highlight Key Outstanding Issues from Last Cycle: AET data was missing and clarity was requested for endotoxin and sterility methods suitability testing.

Remarks: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: The original review of the submission is found in N210605MR01.docx dated March 23, 2018. The Agency issued a complete response letter May 17, 2018 and the applicant's response is covered in this review.

List Number of Comparability Protocols (ANDA only):

This review covers the responses to the deficiencies in the complete response letter sent May 17, 2018.

Antimicrobial Effectiveness Testing

Deficiency (March 13, 2018): The information concerning future plans for additional antimicrobial effectiveness testing (AET) of the 10 mL drug product provided in your March 19, 2018 is acknowledged. However, submission of the AET data in May 2018 will not provide adequate time for Agency review prior to the PDUFA date of May 17, 2018. Successful AET results are required prior to NDA approval. Provide AET results for the 10 mL drug product presentation, which contains polysorbate 20, (b) (4) (b) (4) *at or below the minimum content specification for release or stability testing (whichever is lower). Also, provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch per drug product presentation (i.e. one 3 mL cartridge drug product presentation and one 10 mL vial drug product presentation) at the end of the proposed shelf life. Refer to ICH Q1A Stability Testing of New Drug Substances and Products for new drug products.*

Response from the Applicant (May 11, 2018): (Sequence 0040 1.11.1 Annexure 1-Antimicrobial effectiveness testing for insulin glargine injection (rDNA) 100 IU/mL.pdf)

Preservative effectiveness testing was completed on (b) (4)% label claim (b) (4) for MYL-1501D 10 mL drug product presentation.

Protocol Number: BM/QCM/SD/R/094-01

Acceptance Criteria:

- NLT (b) (4) log reduction for 6 hours as per criteria A for bacteria according to EP.
- NLT (b) (4) log reduction in 24 hours, no requirement for fungi.
- NLT (b) (4) log reduction from the initial count at 7th day for bacteria and no increase from the initial count for fungi as per USP.
- NLT (b) (4) log reduction from the initial count at 14th day for bacteria and no increase from initial count at 14th day for fungi per USP.
- No increase or no recovery for 28th day as per EP for bacteria and fungi.

(b) (4)

(b) (4)

All results meet acceptance criteria of USP <51>

Reviewer's Assessment: ***Adequate***
Antimicrobial effectiveness testing for three lots of the 10-mL vial presentation below the minimum preservative content is provided for three batches of the drug product. The results meet acceptance criteria and test method are adequate. The Applicant also provided AET results for stability studies in both drug product presentations. Please see the stability section for a full review of this commitment.

(b) (4)

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P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary and Conclusion.pdf)
Proposed Expiry: 24 months under refrigeration (5±3°C)

The product stability specification includes the following microbiological tests for both the 3 mL cartridge and the 10 mL vial:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	Must be Sterile
Endotoxin	USP <85>	NMT 80 EU/ 100 units
Seal Integrity	USP <381>	No trace of colored solution.

Long-term Stability storage conditions: 5 ± 3ºC

Test	Time (Months)							
	0	3	6	9	12	18	24	36
Bacterial Endotoxins	X	X	X	X	X		X	X
Sterility	X				X		X	X
Seal Integrity	X				X		X	X

Accelerated Stability storage conditions: 25 ± 2ºC

Test	Time (Months)				
	0	1	2	3	6
Bacterial Endotoxins	X				X
Sterility	X				X
Seal Integrity	X				X

The applicant also intends to perform "in-use" stability testing on the drug product that has been pierced at the seal and stored at 30 ± 2ºC, RH 65 ±5%. The in-use stability test schedules for the cartridge and vial are provided in the tables below.

Cartridge In-Use Stability storage conditions: 30 ± 2ºC, RH 65 ±5% with seal piercing

Test	Time (days)				
	0	7	15	28	31
Bacterial Endotoxins	X				X
Sterility	X				X
AET	X				X

Vial In-Use Stability storage conditions: 30 ± 2ºC, RH 65 ±5% with rubber stopper piercing

Test	Time (days)				
	0	7	15	28	31
Bacterial Endotoxins	X			X	X
Sterility	X			X	X
AET	X				X

Updated the 2/28/2019 submission (Section 1.11.1 Quality Response to FDA Complete Response Letter dated May 17.2018.pdf): The applicant commits to conduct AET for the 3 mL cartridge and 10 mL vial presentation at the end of shelf life. The applicant also plans to update the shelf life of the drug product (b) (4).

Reviewer's Assessment: ***Adequate***
The applicant states that commitment to provided AET data at the end of shelf life in stability studies and will extend these studies (b) (4) (b) (4).

List of Deficiencies:

There are no product quality microbiology deficiencies at this time.

Primary Microbiology Reviewer Name and Date: Jennifer N. Patro 03/19/2019

Secondary Reviewer Name and Date: Elizabeth Bearr 03/19/2019

Jennifer Patro

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Elizabeth Bearr

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/s/

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Recommendation: Complete Response
(Including the Facility Review/Manufacturing Inspection Recommendation)

NDA 210605
Review 1
Review Date: 4/5/18

Drug Name/Dosage Form	Insulin glargine injection/Solution for injection
Trade Name	Semglee and Semglee "Tradename Pen"
Strength	100 units/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Mylan LLC.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and Amendments	*4/27/17 (original) and amendments dated 6/09/17, 6/14/17, 10/16/17, 1/12/2018, 2/16/18, 2/23/1, 2/26/18, 2/28/18, 3/07/18, 3/19/18, 3/20/18, 3/23/18, and 3/28/18*	*Quality (Module 3.2. and 1.1)*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus /Donna Christner	Division of New Drug API/ONDP
Drug Product	Muthukumar Ramaswamy/Danae Christodoulou	New Drug Products II/ONDP
Process	JoAnne Wang/ Chengjiu Hu	Process Assessment/OPF
Microbiology	Jennifer Patro/Elizabeth Bearr	Microbiology Assessment/OPF
Facility (OPF)	Vidya Pai/Brian J Ryan/Juandria Williams	Division of Inspectional Assessment/OPF
Methods Verification	Cynthia Sommers/Connie Ruziicka	Division of Pharmaceutical Analysis/OTR/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products II/ONDP
Facility (CDRH)	Habacuc Barrera	CDRH Compliance
ORA Lead	N/A	N/A
Environmental Analysis (EA)	Muthukumar Ramaswamy	New Drug Products II/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information in the NDA	LOA 1/24/17
	Type III				LOA 11/20/2013
	Type III				1/23/2017
	Type III				1/23/2017
	Type III			Adequate. Refer to microbiology review	1/23/2017
	Type V			Adequate. Refer to microbiology review	LOA 1/23/2017
	Type V				LOA 1/23/17
	Type II			Sufficient information in the NDA	LOA dated 4/26/2017

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105279 and amendments dated 10/22/2012 (Type C meeting), 4/4/2014 (EOP2 meeting), 2/24/2016 (Type C meeting), and 4/7/2016 (Advice/Information request)	Insulin Glargine Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable. (Impurities and Leachables)	3/19/2018	Dr. Lee Elmore
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 12/22/2017	9/6/2017	Habacuc Barrera

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality for NDA 210605 is not to approve the application until the following issues related to manufacturing facility and microbiological control of the product are resolved.

1. FDA's pre-approval inspection of the drug substance and drug product manufacturing facility, Biocon Sdn. Bhd., Malaysia (FEI #3011248248) between Feb.6th -15th 2018 resulted in a withhold recommendation due to objectionable conditions observed at the commercial manufacturing facility. To correct these deficiencies, the Firm has committed to completing several corrective actions (b) (4) (b) (4). Successful completion and implementation of corrective actions is required, before the facility can be considered as acceptable to support the NDA.
2. CMC microbiology review noted the following deficiencies:
   (i) Lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET).
   (ii) Lack of AET data supporting the product expiry from stability.

To resolve these deficiencies, provide the following in your resubmission.

a) Provide AET results for the 10 mL vial drug product presentation (b) (4) at or below the minimum content specification for release or stability testing (whichever is lower).
b) Conduct antimicrobial effectiveness testing per USP <51> or equivalent methodology on at least one primary stability batch corresponding to 3 mL cartridge and 10 mL vial presentation at the end of shelf life. Provide AET results to support the acceptability of the product at the end of expiry.
c) Provide study reports showing actual results to support the suitability of endotoxin, and sterility methods used for analyzing 10 mL vial and 3mL cartridge presentations.

II. Summary of Quality Assessments

A. Product Overview

This NDA is a 505(b)(2) application for recombinant insulin glargine with clinical data. The applicant relies in part on the safety and efficacy information for the listed drug Lantus (insulin glargine injection) 100U/mL approved under NDA 021081. Both the proposed product and the listed drug are clear, colorless solution filled in 10mL vial or in 3mL prefilled pen and are intended for subcutaneous injection. Both products have the same composition and strength. Mylan assigned code for insulin glargine is MYL-1501D.

The applicant provided an analytical similarity comparison between MYL-1501D injection and Lantus using multiple batches of Lantus and MYL-1501D drug product available in vial and pen (cartridge) presentations. The number of batches tested in the analytical comparison between the original and new product was variable. For example, higher order structural comparison studies used at least three batches of drug substance extracted from Lantus or Mylan product. For potency (by HPLC) and purity comparison

a minimum of 5-10 batches of new product were compared with as many as 10-44 batches of Lantus product filled in vial and pen. For bio potency comparison, a minimum of 3-5 batches of the new product against 3-6 batches of original product filled in each presentation.

Due to differences in the proprietary manufacturing process used by Mylan and Lantus manufacturer (e.g., Yeast strain vs. *E.coli* strain for manufacturing the insulin glargine precursor), it is reasonable to expect subtle differences in their product/process related impurity profiles. For example, it is not feasible to compare the levels of impurities such as host cell proteins, single chain precursor or glycosylated variants in MYL-1501D with Lantus as they are inherent to process used to manufacture these products. Impurity profile comparison between Lantus and MYL-1501 D injection is valid for common impurities arising from degradation of insulin glargine during manufacturing and storage (e.g., deamidation, truncation, reactivity towards excipients and reagents (b) (4), (b) (4) to form impurities). The applicant considered these above aspects during immunogenicity risk assessment. Refer to the immunogenicity assessment review.

The analytical similarity exercise provided an assurance that quality characteristics are comparable between Lantus and Mylan insulin glargine injections with respect to primary, secondary, tertiary and higher order structure of insulin glargine, batch release profile, stability profile (real-time, in-use study, accelerated and forced degradation profile), and biological activity (demonstrated by total insulin receptor phosphorylation and IGF-1 receptor binding affinity assays as well as by rabbit blood sugar (USP <121> method).

Drug product review concluded that under long-term conditions both products contained comparable levels of HMWP and individual impurities (b) (4) (b) (4). Under stressed conditions, in addition to above impurities, (b) (4) levels increased in both Lantus and Mylan Process VI batches. Under stressed conditions Lantus batches contained increased levels of (b) (4) (b) (4). For additional details, please refer to analytical similarity assessment of the CMC drug product review dated 3/26/18 in Panorama.

Data from *in vitro* pharmacology studies for Lantus and MYL-1501D is evaluated in the Pharmacology Toxicology review. This NDA is a stand-alone product analogous to other approved insulin glargines and the analytical similarity comparisons are considered as additional supporting information.

The NDA also includes data to show that there is no significant difference in strength, quality or purity between new product and Lantus and meet the standards set in the USP monographs. Biological activity (USP <121> Bioidentity) is part of the regulatory drug substance specification.

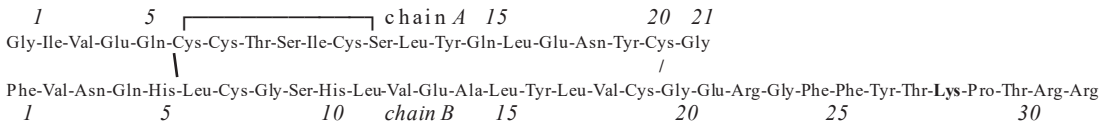
The product is intended for glycemic control in adults and children with diabetes. For maximum daily dose information, please refer to CDTL's memo.

B. Quality Assessment Overview

Drug Substance

Dr. Joseph Leginus has reviewed the CMC information provided for MYL-1501D drug substance and concluded that the drug substance information provided in the NDA is adequate to support the NDA application.

Insulin glargine is produced by recombinant DNA technology utilizing *a Pichia pastoris protein expression system*. Chemically MYL-1501D is 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin. MYL-1501D has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063 Da. MYL-1501D has the same amino acid sequence and structure as the reference listed drug. MYL-1501D has the following structural formula:



MYL-1501D is manufactured from an insulin glargine precursor expressed in *Pichia pastoris protein expression system*. The precursor protein sequence contains a 10 amino acid leader peptide, a modified human insulin B-chain (two arginine to the N-terminal), and modified human insulin A-chain (A 21 glycine instead of asparagine (b) (4)

(b) (4)

During development, the applicant moved the DS and DP manufacturing operation from Biocon Ltd., Bangalore, India (L1) to Biocon Sdn. Bhd., Malaysia (L2). The applicant scaled up the (b) (4) process from (b) (4) (Process V) to (b) (4) (Process VI) and implemented changes to (b) (4) conditions.

The applicant evaluated the analytical comparability of Process V and VI drug substance lots using data from in-process controls, batch release, physicochemical and biological characterization, and stability studies. Per DS substance review, the proposed changes improved the purity of Process VI drug substance without introducing any new impurities. For example, Process VI drug substance contained (b) (4) of glycosylated variants (below limit of quantitation) and (b) (4) total impurities. In comparison, the Process V drug substance lots used in Phase III clinical studies (ED-B13-01-001454, ED-B13-01-001594, and ED-B13-01-001670) contained higher levels of impurities ((b) (4) glycosylated variants and (b) (4) total impurities). Regarding analytical comparability assessment for drug substance, drug substance review commented that a conclusion on analytical comparability of drug substances produced by Process VI and Process V cannot be made due to the significant differences in levels of impurities found in the two different drug substances".

The primary structure of MYL1501D obtained from multiple batches of Process VI drug substance (Process VI batches: BS15005128, BS15005256, BS15005423) was confirmed by

amino acid sequencing, mass spectroscopy (intact and reduced mass) and peptide mapping. Higher order structure was confirmed during analytical similarity by comparing X-ray structure, UV-Vis, near UV and Far UV CD, FT-IR, and NMR spectra of MYL1501 D with that of drug substance extracted from Lantus (batch 4F1179A). Spectral and X-ray structural comparison did not reveal any significant differences. Biological activity of drug substance was demonstrated by total insulin receptor phosphorylation and IGF-1 receptor binding affinity assays as well as by in vivo bioassay (rabbit blood sugar method).

The proposed specifications for insulin glargine conform to USP Insulin glargine monograph. A bioidentity test (rabbit blood sugar by USP <121>) is proposed as part of drug substance specification. Potency of insulin glargine will be determined by mass based HPLC assay. The analytical procedures applied to control the insulin glargine drug substance are essentially those described in United States Pharmacopoeia Monograph or modification of USP methods used for analyzing insulin. The following in-house methods are used for release and are validated: identity (peptide mapping, HPLC retention time), high molecular weight proteins, host cell proteins, host cell DNA, Single-chain precursor, Zinc content, (b) (4) (b) (4), residual solvents (b) (4), assay, related compounds by HPLC (any individual impurity, any individual glycosylated impurity, and total impurities), endotoxin, microbial limits and Bioidentity (USP <121>).

Per drug substance review, the applicant's stability data supported the proposed (b) (4) retest period, when stored (b) (4) (b) (4)

The application contains a comparability protocol for the manufacture and release of a new working cell bank. The applicant committed to compare the stability profiles of at least one commercial scale drug product manufactured from new WCB to the stability of drug product manufactured using current WCB.

Drug substance review concluded that the information is adequate to support the approval of the NDA. For additional details, please refer to Dr. Leginus's review in Panorama under NDA 210605.

Drug Product

Similar to Lantus, MYL-1501 D (Insulin glargine injection) 100 Units/mL is a sterile, aqueous, clear, colorless solution filled in 10mL vial or as 3mL prefilled pen. The potency is based on mass of insulin glargine in solution (100 U = 3.64 mg of insulin glargine). The proposed final formulation is the same as the one used in development and Phase 3 clinical studies.

The drug product contains 3.64 mg of insulin glargine, glycerol (20 mg), metacresol (2.7 mg), zinc (b) (4) (30 mcg; (b) (4)), and water for injection USP. Hydrochloric acid or sodium hydroxide may be added to adjust pH (to 4.0). Similar to Lantus vial presentation, the MYL-1501 D vial product contains 20µg/mL of Polysorbate 20. In comparison to product filled in 3mL cartridge, the 10 mL vial product contains (b) (4) (b) (4)

Zinc and metacresol are provided for [redacted] insulin glargine in solution respectively. The [redacted] drug product are optimized to confer maximum stability during [redacted] ed for use in the drug product are known for use in pharmaceutical products and are not derived from human-animal source.

The drug product filled in USP Type 1 glass cartridge (3mL) contains a [redacted] rubber disc on one end and a [redacted] rubber plunger on the other end. The drug product filled in 10 mL vial contains a [redacted] rubber stopper as closure. The proposed container closure system components are known for use in parenteral products or the same as in approved insulin products and are acceptable for proposed use based on stability data, extractable and leachable information, and seal integrity studies. Pharmacology/ Toxicology Reviewer was consulted on the safety for product related impurities and leachables. No safety concerns were identified.

Dr. Joanne Wang completed the review of the batch formula (drug product), manufacturing process description, process development, and process validation information and concluded that the NDA contains adequate description of the process used for manufacturing MYL-1501 D prefilled pens and vials.

The process used for manufacturing the cartridge and vial presentations was validated at commercial scale [redacted]. With the exception of source of drug substance (Process V vs. Process VI), DP manufacturing site (including equipment), and the batch size [redacted], the proposed commercial manufacturing process and the process used for manufacturing clinical trial batches are similar.

Briefly, the manufacturing process involves [redacted]

Dissolution of active ingredients and excipients and pH adjustment, hold time, [redacted] steps, and visual inspection are considered as critical steps.

The following [redacted] controls are performed on the product. [redacted] tested for pH, assay, visual appearance, assay, bioburden, and endotoxin [redacted], the product is tested for pH and seal integrity. Filled cartridges are tested for friction force test. The applicant performs additional tests [redacted].

MYL-1501 D filled in prefilled pen was used in Phase I PK/PD (Study # MYL-1501D -1001) and Phase III clinical studies (Study: MYL-GAI 3001 and MYL-GAI-3002). Drug product filled in vials was not used in Phase III and Phase I PK/PD studies. With the exception of lot BS15009376, all clinical studies except Phase I PK/PD studies were manufactured at pilot

scale (BS15005852BS15002330, C13DBBFHH-002, C13DBBFHH-004, C14DBBFHH-001 and C14DBBFHH-004)

The applicant provided validation information (b) (4) (b) (4) (b) (4) For detailed information on the manufacturing process and control, please refer Dr. Joanne Wang's review in Panorama dated 3/26/18.

The Applicant utilized risk assessment techniques to identify the critical quality attributes (CQA) of product and assessed the impact of manufacturing process parameters on critical quality attributes. Appearance, Drug content/ Assay, Impurities/ degradants/ Aggregates, (b) (4) (b) (4) Sterility, Endotoxins, Particulate matter, pH, extractable volume, and Leachable/extractable are considered critical quality attributes of the drug product and are part of the proposed product specification. Performance of the pen is verified by friction force test and dose accuracy.

With the exception of the limits proposed for any individual impurity and total impurities, the proposed specification for MYL-1501D insulin glargine injection either conforms to or tighter than the limits proposed in USP monograph for insulin glargine injection and is adequate to assure the quality, strength, and purity of the product. The applicant will be using A HPLC method that is capable of resolving individual impurities better than the USP monograph method. The limits proposed for any individual and total impurities in the drug product specifications are based on maximum age batch used in clinical, and registration stability studies. For a discussion on this topic please refer to CMC drug product review dated 3/23/18.

Analytical procedures proposed for potency and purity are improvements to monograph procedures. All non-compendial analytical procedures (HMWP by HPSEC, assay of Zinc by atomic absorption spectrometry, and assay of (b) (4) related compounds, and insulin glargine content by RP HPLC) were validated. Finished product (Pen injector) specification includes a test for dose accuracy. FDA's Division of Pharmaceutical Analysis (method verification group) evaluated the analytical methods used for assay, HMWP and related compounds and found them to be acceptable. Refer to DPA method verification report in Panorama dated 3/15/18 under NDA 210605.

DPA recommended the following revisions to the HMWP and impurity methods:

a) *Include equations used for impurity calculations to the HPLC and SEC impurity methods.*
b) *Include HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability*.

The critical attributes of the product are controlled through batch records instructions, process design, component specifications, (b) (4) controls (bioburden control, dissolution of excipients, verification of API content, product pH verification, (b) (4) integrity), and through adequate finished product specification. The proposed process control strategy is adequate to assure the quality of the product.

Microbiological controls associated with the drug product manufacturing process were reviewed by microbiology reviewer, *Dr. Jennifer Patro*. Microbiology review covered (b) (4) containers,

closures, equipment and components, (b) (4) validation, environmental monitoring, container closure integrity, antimicrobial effectiveness testing, sterility and endotoxin testing (drug product specification), stability data, and post-approval stability commitment.

Microbiology review identified the following deficiencies:

1) Applicant did not provide product specific method verification information for sterility, endotoxin, and preservative efficacy.
2) The applicant did not conduct antimicrobial testing on product during stability at the end of expiry.

For details, please refer to Microbiology review dated 3/18/18 in Panorama.

Assembly of the disposable pen-injector, testing, packaging, labeling, and release will be performed at Biocon, Bangalore, India. Manufacturing facility compliance status of device assembly site was reviewed by CDRH compliance reviewer and concluded that it is acceptable. A post-approval inspection recommended for the site. *Refer to CDRH Compliance review by Mr. Habacuc Barrera dated 12/22/17 in DARRTS.*

Facility compliance information for drug product and drug substance manufacturing facilities was reviewed by Dr. Vidya Pai. 1. FDA's pre-approval inspection of the drug substance and drug product manufacturing facility, Biocon Sdn. Bhd., Malaysia (FEI #3011248248) between Feb.6th -15th 2018 resulted in a withhold recommendation due to objectionable conditions observed at the commercial manufacturing facility.

To correct these deficiencies, the Firm has committed to completing several corrective actions (b) (4) (b) (4). Per Dr. Pai, successful completion and implementation of corrective actions is required, before the facility can be considered as acceptable to support the NDA.

Her review *concluded that there are outstanding manufacturing or facility risks that prevent the approva*l of this application. Please refer to *the facility review dated 4/4/18 in Panorama for details.*

Expiration Date & Storage Conditions*: Stability data supported a shelf-life of 24 months for the finished product when stored at 2-8 °C. After first use, an in-use period of up to 28 days at room temperature (below 86° F (30 °C) is permitted. Refer to CMC (Drug Product) review dated 3/23/18 in Panorama.*

Shelf-life determination is based on available 6-36 mo. long-term and in-use stability data for Process V and Process VI batches, temperature cycling stability data for commercial scale vial batches (NDA amendment dated 2/16/18), additional individual impurity profile information available for 18 mo. old commercial scale Process VI vials and cartridges (NDA amendment dated 3/19/18), and the stability profile of maximum age of drug product batch used in clinical studies.

The applicant will be asked to seek shelf-life extension based on real-time data for commercial scale Process VI batches.

C. Summary of Drug Product Intended Use: See CDTL's memo.

D. Life Cycle Knowledge Information

Final Risk Assessment - CMC Reviewer's risk assessment for critical attributes is shown at the end of the drug product review. The final risk assessment concluded that the final risk is low for the proposed product. No further mitigation necessary.

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is not recommended for approval.

Muthukumar Ramaswamy, Ph.D. 4/5/18

Application Technical Lead Name and Date

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FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: March 15, 2018

To: Muthukumar Ramaswamy, CMC Lead
Anika Lalmansingh, RBPM

Through: Connie Ruzicka, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Kui Zeng, Ph.D., Chemist, CDER/OPQ/OTR/DPA
Hongping Ye, Ph.D., Research Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 210605: Insulin Glargine, 100 units/mL

The following methods were evaluated and are acceptable with modifications for quality control and regulatory purposes:

1. Assay by HPLC (MYL-1501D, Insulin Glargine-100 U/mL solution for injection from Biocon Sdn. Bhd. (Johor, Malaysia) and pre-filled pen from Biocon Limited (Bangalor, India)

2. Related Compounds by HPLC (MYL-1501D, Insulin Glargine-100 U/mL solution for injection from Biocon Sdn. Bhd. (Johor, Malaysia) and pre-filled pen from Biocon Limited (Bangalor, India)

3. High Molecular Weight Impurity by size exclusion chromatography (MYL-1501D, Insulin Glargine-100 U/mL solution for injection from Biocon Sdn. Bhd. (Johor, Malaysia) and pre-filled pen from Biocon Limited (Bangalor, India)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

1. The HPLC and High Molecular Weight Impurity (SEC) methods did not include equations for impurity calculations. Therefore, the DPA reported impurities as a relative percentage of peak areas. The DPA recommends adding a legend of equations for impurity calculations to the HPLC and SEC impurity methods.

2. The system suitability for the HPLC impurity method did not have peak resolution criteria. DPA recommends adding HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability.

3. The DPA was asked to evaluate thermally stressed drug product samples (40ºC 75% RH for 1 week) in each of the requested methods. The stressed samples (vials and pre-filled pens) were prepared by the applicant (Mylan GmbH) and sent to DPA for analysis. The % of Impurities 2, 3 and 4 and Total Impurities increased to detection levels, but where within the specification limits. Of note, the resolution of two of the impurities to insulin were less than (b) (4) in the stressed samples. The DPA recommends a resolution of not less than 2.0.

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8819fc8f4

Test Samples			Vial (10 mL/vial)		Pen (3 mL/vial)		Vial, stressed sample		Pen, stressed sample	
Method	Test Item	Specification	Result	**Pass/Fail**	Result	**Pass/Fail**	Result	**Pass/Fail**	Result	**Pass/Fail**
1. Analytical Procedures-Assay by HPLC (MYL-1501D Insulin Glargine).	Assay		(b) (4)	**Pass**	(b) (4)	**Pass**	(b) (4)	**Pass**	(b) (4)	**Pass**
2. Analytical Procedures Related Compounds by HPLC (MYL-1501D Insulin Glargine).	Impurity 1			**Pass**		**Pass**		**Pass**		**Pass**
	Impurity 2			**Pass**		**Pass**		**Pass**		**Pass**
	Impurity 3			**Pass**		**Pass**		**Pass**		**Pass**
	Impurity 4			**Pass**		**Pass**		**Pass**		**Pass**
	Impurity 5			**Pass**		**Pass**		**Pass**		**Pass**
	Impurity 6			**Pass**		**Pass**		**Pass**		**Pass**
	Total Impurity			**Pass**		**Pass**		**Pass**		**Pass**
3. Determination of high molecular weight impurity by SEC (MYL-1501D Insulin Glargine).	HMWP			**Pass**		**Pass**		**Pass**		**Pass**
Note: (b) (4)										

PROCESS

Review Recommendation: Adequate from Process Perspective

Product Background: Two presentations are proposed. Presentation one: Combination drug product. 100 U/mL of insulin glargine and is presented in a pre-filled pen integrated with 3-mL colorless tubular glass (USP Type 1) cartridges that are sealed using (b) (4) (b) (4) seals and plugged with (b) (4) plunger stoppers. Presentation two:100 units/mL of insulin glargine presented in a 10 mL clear tubular glass (USP Type 1) vial closed with a (b) (4) rubber stopper and sealed using a flip-off seal. This is a **(505(b)(2) relied on NDA 021081.**

Proposed Indication: SEMGLEE is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

NDA: 210605

Drug Product Name / Strength: SEMGLEE. Insulin glargine (rDNA origin) – 100 U/mL.

Route of Administration: Solution for subcutaneous injection.

Applicant Name: Mylan GmbH

Review Summary:

Presentation I: The manufacturing process for MYL-1501D drug product (DP) in cartridges involves (b) (4) (b) (4)

Presentation II: The manufacturing process for MYL-1501D drug product (DP) in 10 mL vial presentation involves (b) (4) (b) (4)

pH of the final formulation is a critical process parameter for the DP process for both presentations. (b) (4) (b) (4). Adequate supporting data and development work has been performed to justify the proposed pH control range during manufacturing (b) (4)

(b) (4)

No scale up is proposed for commercial batches. The Phase 3 pivotal clinical studies were conducted with DP manufactured at the Bangalore India (L1) manufacturing site, which is different from the proposed commercial Malaysia (L2) site that manufactured the stability batch. Based on information provided by the applicant, we found there was only scale difference but no critical process change was noted.

List Submissions being reviewed (table):

Document(s) Reviewed	Date Received
NDA Original Application	April/27/2017
CMC IR Request Response (Sequence 0015)	10/16/2017
Response to CMC IR Dated Jan 15 2018 (0029)	02/28/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

P.3 Manufacture

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Joanne Wang

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Chengjiu Hu

Digitally signed by Chengjiu Hu
Date: 3/26/2018 02:15:06PM
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MICROBIOLOGY

Product Background:

NDA/ANDA: NDA 210605

Drug Product Name / Strength: MYL-1501D (Insulin Glargine) 100 U/mL SEMGLEE

Route of Administration: intramuscular injection

Applicant Name: Mylan

Manufacturing Site: Biocon Sd. Bhd. (930330-U)
No. 1, Jalan Bioteknologi 1,
Kawasan Perindustrian SiLC,
79200 Iskandar Puteri, Johor, Malaysia

Method of Sterilization: (b) (4)

Review Recommendation: The submission **is not recommended** for approval on the basis of product quality microbiology.

Review Summary: This is a sterile solution filled into 10 mL vials or 3 mL cartridges (pre-filled pens). (b) (4)

(b) (4)

List Submissions Being Reviewed: 04/27/2017, 2/16/2018 IR response, 2/28/18 IR response, 3/19/18 IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This application is being filed under protest with the Agency. However, a normal review process will take place.

Concise Description Outstanding Issues Remaining: Lack of endotoxin method suitability data, lack of sterility method suitability data, and lack of AET testing data and AET testing during stability.

Supporting Documents: Microbiology review (b) (4) (dated 9/22/2016 is referenced (b) (4) and is found adequate.

DMF (b) (4): A LOA was provided for DMF (b) (4) dated January 23, 2017 for the (b) (4) and found adequate.

DMF (b) (4): A LOA dated January 23, 2017 was provided for DMF (b) (4) (b) (4) and found adequate.

(b) (4) validation data (b) (4) was previously reviewed in (b) (4) on May 9, 2017.

DMF (b) (4): A LOA dated January 30, 2009 was provided for DMF (b) (4) (b) (4) and found adequate.

List Number of Comparability Protocols (ANDA only): N/A

(b) (4)

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Jennifer Patro

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Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 3/26/2018 04:43:34PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

John Arigo

Digitally signed by John Arigo
Date: 3/26/2018 07:53:02AM
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/s/

ANIKA A LALMANSINGH
12/22/2017
Uploaded on behalf of Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB