

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210605Orig1s000

SUMMARY REVIEW

CDTL Review and Division Summary Memo for Regulatory Action

Date	June 11, 2020
From	Patrick Archdeacon, M.D.
NDA #	210605
Applicant	Mylan
Date of Submission Receipt	December 16, 2019
PDUFA Goal Date	June 16, 2020
Established (USAN) names	Insulin glargine injection
Trade names	Semglee
Dosage forms / Strength	Solution for sc injection / 100 units/mL
Proposed Indication	To improve glycemic control in adults and children with type 1 diabetes mellitus and adults with type 2 diabetes mellitus
Recommended Action	Approval

1. Introduction

This document contains the ‘Summary Basis for Regulatory Action’ memo for the second resubmission of NDA 210605 for Mylan’s proposed insulin glargine (also known as MYL-1501D, proposed proprietary name: Semglee) disposable pen presentation and vial presentation. Mylan (hereafter referred to as the Applicant) submitted the NDA through the 505(b)(2) regulatory pathway. FDA issued a Complete Response Letter (CRL) to the original submission of NDA 210605 on May 17, 2018 and issued a second CRL to the initial resubmission of NDA 210605 on August 28, 2019. While the first CRL included clinical-related major deficiencies, human factors-related major deficiencies, and product quality-related major deficiencies, the second CRL included only product quality-related major deficiencies. The Applicant submitted the second resubmission on December 16, 2019 to address the remaining product quality-related deficiencies.

The second resubmission includes responses to the product quality-related major deficiencies, cited in the second CRL issued to the initial NDA submission. As described in this memo, the product quality reviewers concluded (and I concur) that the resubmission adequately addressed the product quality-related major deficiencies cited in the second CRL. Further, I concur with the recommendation of the integrated product quality review to approve NDA 210605 (insulin glargine/Semglee).

Each proposed presentation in this 505(b)(2) application relies, in part, on FDA’s finding of safety and effectiveness for Lantus and Lantus Solostar (NDA 21081; insulin glargine injection), which are collectively described as “Lantus” in this review. Lantus was initially approved on April 20, 2000. Lantus is 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 describes the use of MYL-1501D in combination with the (b) (4) disposable pen; this presentation of MYL-1501D is therefore a combination product. NDA 210605 also includes a presentation of MYL-1501D in a 10 mL vial.

In the second CRL, FDA stated that, as explained in FDA’s final guidance on *Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 [BPCI Act]*, “an original 505(b)(2) application (including a resubmission) for a biological product that relies, at least in part, on FDA’s finding of safety and/or effectiveness for a listed drug that is a biological product will receive a complete response if the application is pending at the end of the day ... on Friday, March 20, 2020, because the NDA for the listed drug relied upon will no longer exist at midnight on Monday, March 23, 2020.” This reflected the requirement in section 7002(e)(4) of the BPCI Act that, on March 23, 2020, an approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (such as insulin glargine) shall be deemed to be a license for the biological product (i.e., an approved biologics license application (BLA)) under section 351 of the Public Health Service Act (PHS Act). However, on December 20, 2019, the Further Consolidated Appropriations Act, 2020 (FCA Act) was enacted and, among other things, amended section 7002(e)(4) of the BPCI Act to provide that FDA will continue to review an

application for a biological product under section 505 of the FD&C Act after March 23, 2020, so long as that application was submitted under section 505 of the FD&C Act, is filed not later than March 23, 2019, and is not approved as of March 23, 2020 (see section 607 of the FCA Act). As amended, the statute provides that only for purposes of carrying out this continued review, any drug that is a biological product that has been deemed licensed under section 351 of the PHS Act and that is referenced in such a pending application shall continue to be identified as a listed drug in the Orange Book. The statute further provides that if such a pending application is approved under section 505 of the FD&C Act before October 1, 2022, it will be deemed to be a license for the biological product upon approval. Accordingly, NDA 210605 will be approved under section 505 of the FD&C Act. However, upon approval, NDA 210605 will be deemed to be an approved BLA under section 351(a) of the PHS Act.

The reader is referred to the individual discipline reviews and to the reviews of the original NDA submission for a more comprehensive discussion of the MYL-1501D development program.

This memo references the following documents/sources:

Subject	Author	Date
DMEPA revised label review	Ariane Conrad	March 5, 2020
DMEPA Proprietary Name Review	Ariane Conrad	February 3, 2020
OPDP review	Ankur Kalola	April 10, 2020
Patient Labeling Team	Ankur Kalola, Nyedra Booker	April 15, 2020
OPQ review	Vidya Pai (Facility), Muthukumar Ramaswamy (Application Technical Lead)	May 22, 2020
DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; OPQ: Office of Pharmaceutical Quality		

2. Background

NDA 210605 was originally submitted on April 27, 2017. FDA refused to file the original submission because the drug product (MYL-1501D Process V) used in the submitted PK/PD clamp studies and the pivotal phase 3 trials was manufactured using a different process than the drug product intended to be marketed (MYL-1501D Process VI). The Applicant stated that they adopted Process VI in response to advice from the European Medicines Agency (EMA) to reduce impurities in the drug substance: the use of Process VI reduces (b) (4) of insulin glargine compared to Process V. However, at the time of the original submission, the Applicant did not include data that adequately bridged MYL-1501D Process V and MYL-1501D Process VI. This deficiency was identified prior to the original NDA submission and was communicated to the Applicant both prior to the original NDA submission and as part of a Refuse-to-File decision.

On August 15, 2017, a Type A meeting was held to discuss the Refuse-to-File decision. At that meeting, the Applicant was informed that they could request that the application be Filed Over Protest and that the Agency would be obliged to review the application. At that meeting, the Applicant was also advised to conduct an 18-week clinical study to support a bridge between the Process V and Process VI drug products. On August 31, 2017, the Applicant requested that its NDA be Filed over Protest. Accordingly, the NDA was filed over protest on September 15, 2017 (60 days after the date on which the Applicant requested the meeting described above) and FDA completed the review of the original NDA submission. On September 19, 2017, the Applicant submitted a clinical protocol to IND 105279 for an 18-week clinical bridging study.

FDA issued a CRL on May 17, 2018 in response to the original NDA submission. The deficiencies cited in the CRL included, but were not limited to, the absence of adequate bridging data to establish that the clinical trial data generated with MYL-1501D Process V are relevant to MYL-1501D Process VI and can be used to support a determination that the proposed to-be-marketed product (i.e., MYL-1501D Process VI) is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

Other deficiencies cited were:

- The absence of bridging data necessary for approval of the vial presentation of MYL-1501D.
- Objectionable findings during inspection of the manufacturing facility (Biocon Sdn. Bhd. FEI#3011248248).
- Lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET).
- Lack of AET data supporting the product expiry from stability.
- Human factors-related major deficiencies.

The Applicant resubmitted NDA 210605 on February 28, 2019. The resubmission package included data from two new euglycemic clamp PK/PD studies (MYL-1501D-1003: comparing MYL-1501D Process V, MYL-1501D Process VI, and US-approved Lantus; MYL-1501D-1004: comparing cartridge and vial formulations of MYL-1501D Process VI) and a new efficacy and safety study conducted in patients with type 1 diabetes mellitus (MYL-1501D-3004: comparing MYL-1501D Process V and MYL-1501D Process VI). MYL-1501D-3004 was conducted to provide adequate bridging data to establish that the clinical trial data generated with MYL-1501D Process V are relevant to MYL-1501D Process VI. MYL-1501D-1004 was conducted to bridge the prefilled pen and vial presentations. MYL-1501D-1003 did not address any deficiencies cited in the CRL, but confirmed the conclusions based on the review of MYL-1501D-1001. The resubmission also included responses to the other deficiencies cited in the CRL, including corrective and prevention actions (CAPA) execution updates to address the inspection findings, AET method validation, additional CMC data, the results of an additional human factors pediatric validation study, and an additional differentiation study.

Based on review of the February 28, 2019 NDA resubmission, Office of Pharmaceutical Quality (OPQ) continued to recommend approval based on the drug substance, drug product, and manufacturing process reviews and further determined that the microbiology issues were

resolved, but the pre-approval inspection of the facility between June 24, 2019 and July 5, 2019 again resulted in a “withhold recommendation.” All other review disciplines determined that the February 28, 2019 NDA resubmission resolved the major deficiencies cited in the original May 17, 2018 CRL. On August 28, 2019, FDA issued a second CRL describing the remaining OPQ deficiencies. On December 16, 2019, the Applicant submitted its second NDA resubmission to address the major deficiencies cited in the second CRL.

3. CMC/Device

OPQ performed the overall quality/CMC review for the original submission, as well as both resubmissions, of NDA 210605. At the time of the original submission, the drug substance, drug product, and process reviews recommended approval. At the time of the first resubmission, OPQ determined that the microbiology issues were resolved. Similarly, Dr. Rong Guo from the Center for Devices and Radiologic Health (CDRH) previously recommended approval of the device constituent of the combination product. The pre-approval inspection of the drug substance and drug product manufacturing facility (Biocon Sdn. Bhd., FEI#3011248248) conducted between June 24, 2019 and July 5, 2019 as part of the first NDA resubmission review resulted in a “withhold recommendation” from Office of Regulatory Affairs (ORA) due to objectionable conditions observed.

The second NDA resubmission contained the Applicant’s response to the product quality deficiencies outlined in the August 28, 2019 CRL and indicated that the manufacturing site in Biocon Sdn., Bhd., Malaysia is ready for inspection. The response further indicated that Biocon Sdn., Bhd., has implemented corrective and preventive actions (CAPAs) to address FDA’s concerns. FDA re-inspected the Biocon Sdn. Bhd. Manufacturing facility located in Malaysia (FEI #3011248248) between February 10, 2020 and February 21, 2020.

OPQ and CDRH continue to recommend approval based on the drug substance, drug product and process reviews, microbiology, and device reviews (see reviews from previous submissions for details). Further, Dr. Vidya Pai, the OPQ facility reviewer, concluded based on the review of the facility information associated with the second resubmission (including the Applicant’s response to the most recent FDA Form 483 observations) that the results of the most recent pre-approval inspection (PAI) support an overall recommendation of approval for facilities associated with the second NDA resubmission. I concur with her recommendation. Dr. Muthukumar Ramaswamy, the OPQ Application Technical Lead, concluded that from the CMC perspective, NDA 210605 is recommended for approval. I also concur with his recommendation.

Facility Compliance

Dr. Vidya Pai reviewed the facility compliance information for drug product and drug substance manufacturing facilities for the site in Malaysia (FEI#3011248248). The pre-approval inspection of the L2 site conducted between June 24, 2019 and July 5, 2019 for the previous review cycle resulted in a “withhold recommendation” from Office of Regulatory Affairs (ORA) due to objectionable conditions observed. The June 24, 2019 through July 5, 2019 inspection resulted in the issuance of a 12-item Form FDA 483. Several of the items cited on the Form 483 were repeat observations from the inspection associated with the

original review. (b) (4)

(b) (4). To correct the deficiencies, the Applicant had committed to completing CAPAs (b) (4)

The follow-up PAI associated with the second NDA resubmission occurred between February 10, 2020 and February 21, 2020. The inspection focused on a review of the implementation and effectiveness of the CAPAs and also included an assessment of overall quality systems to support drug substance and product manufacturing/testing operations. Of twelve observations associated with the previous PAI, two observations were deemed likely to require additional follow-up by the onsite inspector (b) (4)

(b) (4). Overall, the inspection resulted in a 3-item FDA Form 483 with an initial field recommendation of voluntary action indicated (VAI) and a recommendation to approve the application. Dr. Pai concurred with the initial field recommendation. She made no recommendations for post-approval commitments, but recommended post approval inspections 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#4007160792 (Device Coverage IDD)

Nonclinical Pharmacology/Toxicology

The second NDA resubmission includes no new nonclinical data. In the original submission, Dr. Arulananam Thilagar reviewed the nonclinical data submitted to the NDA. He found that the pharmacology/toxicology data supports a determination that NDA is approvable; I concur with his recommendation.

The Applicant conducted in vitro pharmacology assays, in vivo pharmacodynamic (PD) and pharmacokinetic (PK) studies, along with in vitro insulin receptor (IR), insulin-like growth factor-1 receptor (IGF-IR) binding studies, cell-based receptor-dependent metabolism and mitogenicity studies, and a repeat-dose rat toxicity study to compare MYL-1501D and US-approved Lantus. The Applicant conducted many nonclinical studies with MYL-1501D Process V drug substance in addition to the head-to-head nonclinical in vitro and in vivo studies with MYL-1501D Process VI and US-approved Lantus that were found by Dr. Thilagar to provide adequate support to the NDA submission. The review of the submitted studies evaluated all the in vitro and in vivo toxicology studies comparing MYL-1501D Process VI and US-approved Lantus. Dr. Thilagar found that those pharmacology/toxicology data support the similarity of MYL-1501D Process VI and US-approved Lantus. Dr. Thilagar did not review all of the nonclinical studies that used formulations different from the Process VI MYL-1501D formulation or performed with comparators other than US-approved Lantus. Please see Dr. Thilagar's review of the original NDA, dated April 10, 2018, for details.

The toxicology studies bridging MYL-1501D Process VI and Lantus support an abbreviated non-clinical development program and provide an adequate scientific justification for reliance on FDA's finding of safety for Lantus as reflected in product labeling that describes, among other things, reproduction and early development, carcinogenicity, and chronic toxicology studies.

4. Clinical Pharmacology/Biopharmaceutics

The second NDA resubmission includes no new clinical pharmacology data. Dr. Jing Niu evaluated the clinical pharmacology data for both the original submission and the resubmission of NDA 210605. Dr. Niu concluded that two euglycemic clamp studies (MYL-1501D-1001 and MYL-1501D-1004) each independently demonstrated PK/PD similarity across MYL-1501D Process V, MYL-1501D Process VI, and US-approved Lantus. She also concluded that PK/PD study MYL-1501D-1004 established PK/PD comparability between MYL-1501D Process VI vial presentation (with polysorbate) and MYL-1501D Process VI cartridge/pre-filled pen presentation (without polysorbate). I concur with Dr. Niu's conclusions. See Dr. Niu's previous reviews for additional details.

5. Clinical/Statistical- Efficacy

The second NDA resubmission includes no new clinical pharmacology data. In the original NDA submission, Dr. Anna Ketterman and Dr. Mitra Rauschecker evaluated the clinical trial data from MYL-GAI-3001 (patients with T1D) and MYL-GAI-3002 (patients with T2D). Those trials established the non-inferiority of MYL-1501D Process V to Lantus. In the first NDA resubmission, Dr. Anna Ketterman and Dr. Sonia Doi evaluated the new clinical trial data from MYL-1501D-3004 submitted to the NDA. Both Dr. Ketterman and Dr. Doi concluded, and I concur, that the submitted data demonstrate the non-inferiority of MYL-1501D Process VI to MYL-1501D Process V, based on change in HbA1c from baseline to Week 18 when administered in combination with mealtime insulin lispro. Please see the previous reviews of Drs. Ketterman and Doi for additional details.

6. Safety

The second NDA resubmission includes no new data. In the original NDA submission, Dr. Dr. Mitra Rauschecker evaluated the clinical trial data from MYL-GAI-3001 (patients with T1D) and MYL-GAI-3002 (patients with T2D) from the perspective of safety. In the first NDA resubmission, Dr. Doi evaluated MYL-1501D-3004 from the perspective of safety, including immunogenicity. Overall, Drs. Rauschecker and Doi concluded (and I concur) that the safety findings for MYL-1501D were consistent with the known safety profile of Lantus. Dr. Doi also concluded (and I concur) that the data from MYL-1501D-3004 provide sufficient additional clinical safety and efficacy bridging data, including an assessment of immunogenicity (in combination with the PK/PD data from MYL-1501D-1001 and MYL-1501D-1003 that demonstrate PK/PD similarity between MYL-1501D Process V and MYL-1501D Process VI) to establish that the efficacy and safety data generated with the Process V

drug product is relevant to the Process VI drug product (i.e., the to-be-marketed product). Together, these data support a determination that the proposed to-be-marketed product is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus. Please see the previous Clinical reviews for additional details.

7. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

8. Pediatrics

The Division determined that this NDA does not trigger the Pediatric Research Equity Act. Therefore, a pediatric assessment is not required.

9. Labeling

The second NDA submission include minor revisions to labeling previously reviewed during the prior cycle.

Ariane Conrad from the Division of Medication Error Prevention and Analysis (DMEPA) conducted a review of the revised labels and labeling. Based on her review, the Applicant was advised to add the statement "Dispense in this sealed carton" to the Principal Display Panel (PDP) to decrease the risk of improper dispensing of the product. After the Applicant implemented the recommendation, she found that the revised labels and labeling for Semglee were acceptable from a medication error perspective and I concur with her conclusion. During the prior review cycle, DMEPA reviewed a differentiation study to confirm that the intended user population can differentiate the Semglee pre-filled pen from the Humulin R U-500 KwikPen, using the proposed Semglee labeling, because the proposed Semglee pre-filled pen and the Humulin R U-500 KwikPen (500 units/mL) are similar in appearance. While the differentiation study did not exclude the possibility of errors due to confusing the two pens, the Applicant subsequently provided an assessment that suggested that this would be "highly unlikely." The FDA Clinical Review team agreed that the likelihood of these medications being concomitantly prescribed was low. Please see the relevant reviews from the previous review cycle for details.

Ankur Kalola, PharmD, from Office of Prescription Drug Promotion (OPDP) conducted a review of a revised Package Insert (PI) included in the December 16, 2019 NDA resubmission. While the PI had been previously evaluated during the prior review cycle, revisions had been made to incorporate relevant information from updated labeling for Lantus approved November 15, 2019.

Nyedra Booker, PharmD, from the Division of Medical Policy Programs (DMPP), and Ankur Kalola also reviewed revisions to the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) included in the December 16, 2020 NDA resubmission. Their collaborative

review recommended several changes to the Applicant to simplify and clarify language in the PPI and IFU.

Please see the reviews for this second NDA resubmission by Ariane Conrad, Ankur Kalola, and Nyedra Booker for details.

10. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend **Approval**

- Post-marketing requirements

None

- Post-marketing commitments

As per recommendations from OPQ, I recommend post approval inspections for the following sites:

1. [REDACTED] ^{(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#4007160792 (Device Coverage IDD)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
06/11/2020 10:19:18 AM