CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208157Orig1s000

CLINICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCHIN
Division of Metabolism and Endocrinology Products
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MEMORANDUM

FROM:	Frank Pucino, PharmD, MPH Clinical Reviewer Division of Metabolism and Endocrinology Products (DMEP)
THROUGH:	Patrick Archdeacon, MD Acting Clinical Team Leader, DMEP
SUBJECT:	Clinical Review — NDA 208157 (Regular human insulin in 0.9% sodium chloride injection)
APPLICANT	Celerity Pharmaceuticals, LLC
RECEIPT DATE:	August 22, 2018
PDUFA GOAL DATE:	June 22, 2019
REVIEW DATE:	(See electronic signature)

This memorandum serves the purpose of the Clinical Review of New Drug Application (NDA) 208157 (regular human insulin in 0.9% sodium chloride injection [MYXREDLIN]). For this Application, no Phase 3 efficacy and safety clinical trials were planned or conducted. The only clinical data submitted was from a single Phase 1 biopharmceutics study (i.e., CEL-HI-200). Additionally, at the pre-IND meeting (PIND 124943; dated May 22, 2015), the Applicant was asked to submit justification for why immunogenicity assessments would not be necessary for this product. This justification was provided in the Clinical Overview submitted with the Application.[1] A brief executive summary of the clinical information relevant to the current submission will be presented.

[1] Applicant's Clinical Overview, Section 3, pages 6-12, available at: \\cdsesub1\evsprod\nda208157\0000\m2\25-clin-over\clinical-overview-208157-us.pdf

1. Recommendation on Regulatory Action

I recommend approval of this NDA pending agreement on labeling.

2. Introduction and Regulatory Background

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1D; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2D; characterized by β-cell dysfunction and resistance to insulin activity with inadequate insulin production to maintain euglycemia).[1,2] According to the 2017 National Diabetes Statistics Report, diabetes affects an estimated 30.3 million people within the United States (U.S.),[3] of which T2D accounts for 90-95% of all diagnosed cases.[3,4] As of 2013, diabetes also is the most expensive medical condition to diagnose and treat in the U.S., accounting for $101.4 billion in healthcare spending.[5]

Patients with T1D may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2D can be asymptomatic. As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications.[6,7] For patients with T2D, the presence of microvascular and macrovascular disease are independently associated with a 10-year risk of death, major adverse cardiovascular events (MACE: nonfatal myocardial infarction, nonfatal stroke, or CV death), and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness), while coexistence of both micro- and macrovascular disease is associated with a 2.0-, 2.9- and 6.3-fold greater risk of these complications, respectively.[8] Diabetes remains a leading cause of kidney failure,[9] adult-onset blindness,[10,11] and non-traumatic lower limb amputations.[12,13] Additionally, people with diabetes are more than twice as likely to have cardiovascular disease (CVD) or stroke as nondiabetic individuals—and at an earlier age.[14,15] Several reports suggest that CVD may affect approximately 40% of T1D patients over 65 years of age and 32% of persons with T2D.[16] Diabetes was the seventh leading cause of death in 2015,[3] and CVD remains a major cause of death among diabetics. Based on the results of the Diabetes Control and Complication Trial (DCCT),[17-23] the United Kingdom Prospective Diabetes Study (UKPDS),[7,24-27] and the Kumamoto Study,[28] improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

Exogenous administration of insulin is the mainstay of antihyperglycemic therapy in T1D, and it is also used to improve glycemic control in patients with T2D.[29] There are numerous insulin products commercially available in the U.S.[29]

The Applicant, Celerity Pharmaceuticals, is requesting approval of MYXREDLIN (regular human insulin in 0.9% sodium chloride injection) for the indication to improve glycemic control in adult and pediatric patients with T1D and T2D. This NDA is being submitted as a 505(b)(2) application that relies, in part, on the Food and Drug Administration's (FDA's) finding of safety and effectiveness for the listed drug NOVOLIN R (regular human insulin injection; NDA 019938, Novo Nordisk Inc.)[30] for approval. The proposed commercial presentation of the Celerity insulin product consists of a 100 mL GALAXY bag containing 100 units of regular human insulin/100 mL of 0.9% sodium chloride. The product is intended to be administered by intravenous (IV) administration in a hospital or emergency room setting using commercially available insulin infusion sets.

A brief summary of the relevant regulatory history of NDA 208157 is provided in (Table 1).

Table 1: Summary of Presubmission/Submission Regulatory History for NDA 208157

Date	Summary of Relevant Agency Interactions
June 25, 1991	NDA 019938 – FDA approves NOVOLIN R (insulin human injection), the listed drug for NDA 208157 (MYXREDLIN), to improve glycemic control in adults and pediatric patients with diabetes mellitus.
April 22, 2015[a]	PIND 124943 – Applicant submits a Type B Meeting Briefing Package.
May 22, 2015[b]	PIND 124943 – FDA provided advice to the Applicant for the MYXREDLIN development program summarized as follows: • Establish an adequate scientific bridge between MYXREDLIN and NOVOLIN R to demonstrate that reliance is scientifically justified, with data to support any modifications to the listed drug. • Submit a nonclinical GLP-compliant toxicity study with TK assessment to support reliance on the listed drug for nonclinical safety. • Regarding data to be included in the initial IND submission, product-specific impurities, product-related substances, and process-related impurities should be identified, characterized, and compared in a side-by-side table format to the listed product, in addition to chromatograms. • The data package for NDA submission should include additional characterization data to compare quaternary structures of the two products using standard methods. The stability data to compare degradation profiles and biological activities should include long-term and accelerated storage conditions, stress conditions and in-use conditions. • Provide a plan to assess product immunogenicity and determine whether it impacts PK or clinical outcomes or provide justification why immunogenicity assessments would not be necessary. If assessments are needed, the proposed Clinical Pharmacology study (i.e., crossover design in healthy volunteers) would not be appropriate to evaluate immunogenicity.
December 11, 2015[c]	IND 124943 – Applicant submits the iPSP, requesting a waiver of pediatric studies.
February 4, 2016[d]	IND 124943 – FDA informed the Applicant that none of the criteria under 21 U.S.C. 355c[31] applied to their product, and therefore, they were exempt from PREA requirements.

March 31, 2017[e]	IND 124943 – Applicant submits their IND (Study CEL-HI-200).
May 16, 2017[f]	IND 124943 – FDA issued a 'Study May Proceed Letter' stating that they did not recommend that the Applicant perform immunogenicity analysis for the proposed Phase 1 study at this time. However, it was recommended that they collect and bank serum samples at baseline, prior to each of the two insulin infusions, and one month after the last infusion. Should assessment of immune response to their product be requested, they should develop and validate assays for detecting and confirming anti-drug antibodies (ADAs). An assay to establish ADA titers also was recommended.
May 16 2017[g]	IND 124943 – Applicant requested review of the proposed proprietary name, MYXREDLIN.
May 16 2017[h]	IND 124943 – FDA concluded that the proposed proprietary name was conditionally acceptable.
May 30, 2017[i]	IND 124943 – Applicant submits protocol amendment #1 to Study CEL-HI-200 (i.e., change in blood sampling volume from 410 mL to 515 mL for the PK and C-peptide testing due to a change in the testing facility sites from (b) (4), (b) (4) to (b) (4).
June 29, 2017[j]	IND 124943 – Applicant submits protocol amendment #2 to include additional sampling requirements for possible immunogenicity testing (i.e., 5 mL blood samples collected at Screening, prior to each of the two insulin infusions, and at the end of study, and stored for possible future immunogenicity analysis).
April 26, 2018[k]	NDA 208157 – Applicant submits their Application for MYXREDLIN.
May 10, 2018	NDA 208157 – The Application was not accepted for filing due to non-payment of PDUFA fees.
May 16, 2018[l]	NDA 208157 – FDA informs Applicant that all required fees were accepted, and the new Application receipt date was May 4, 2018.
July 2, 2018[m]	NDA 208157 – FDA issues a Refusal to File letter for the following reasons: 1. NDA Section 3.2.P.3.5.2.3, Process Performance Qualification, does not contain prospective validation results for three consecutive drug product lots produced at the commercial scale (i.e., possible risk that the drug product produced by the commercial process may not be comparable to the clinical process). The NDA section states that, "process performance qualifications will be conducted in conjunction with or prior to the production of commercial batches according to a validation protocol." The validation results are needed in the original NDA to demonstrate that the commercial manufacturing process is suitable for its intended purpose. 2. In the Type B written responses for PIND 124943 (dated May 22, 2015), FDA recommended that a GLP-compliant bridging toxicity study comparing MYXREDLIN with U.S.-approved NOVOLIN R be conducted and submitted with the NDA to support the scientific appropriateness of reliance on FDA's finding of safety and/or effectiveness for NOVOLIN R to support the nonclinical safety of the proposed product. (b) (4)

July 12, 2018[n]	NDA 208157 – Addendum to the Pharmacology/Toxicology Filing Memorandum. Following clarification from the Applicant that a 2-week bridging toxicity study to evaluate insulin-related impurities was conducted in agreement with the Division (email correspondence dated 5/3/2017) (b) (4) (b) (4) the Pharmacology/Toxicology review team considered that the nonclinical data submitted was sufficient to support NDA filing.
July 17, 2018[o]	NDA 208157 – Applicant submits a Type A Meeting Request and briefing package to address remaining filing issues.
August 16, 2018[p]	NDA 208157 – Type A Meeting. FDA informed the Applicant that to consider applications for biotechnology products complete, process validation results are typically provided to demonstrate that the commercial process (i.e., (b) (4) L, which is (b) (4) -fold greater than the clinical process) consistently produces drug products with the quality and stability characteristics that the product is purported to possess. Therefore, the NDA submission is incomplete because it did not contain analytical data sufficient to conduct a scientific review with respect to whether the clinical drug product material is comparable to the proposed commercial product. During the meeting, the Applicant proposed to use a (b) (4) clinical process as a new commercial process which was identical to the clinical process described in their NDA. They planned to initiate the PPQ approximately 4-5 months prior to the anticipated approval date. The PPQ for 3 lots would be completed prior to commercial distribution and results submitted to FDA. The PPQ protocol would be available prior to midcycle of the review period. The FDA agreed that the Applicant's proposal to resubmit the Application using a [redacted] commercial scale to address the filing issue would be acceptable.
August 22, 2018[q]	NDA 208157 – Applicant resubmits their Application for MYXREDLIN.

Source: Adapted from the following submissions:

a. Applicant's PIND 124943 Type B Meeting Briefing Package, available at: \\cdsesub1\evsprod\ind124943\0000\m1\us\briefing-package.pdf
b. Applicant's PIND Meeting Responses, available at: \\cdsesub1\evsprod\nda208157\0000\m1\us\correspondence-pre-ind.pdf
c. Applicant's Pediatric Study Plan, available at: \\cdsesub1\evsprod\ind124943\0001\m1\us\pediatric-study-plan.pdf
d. Applicant's Other Correspondence Regarding Pediatric Exclusivity Study Plans, available at: \\cdsesub1\evsprod\nda208157\0000\m1\us\other-corresp-regarding-pediatric-exclusivity-study-plans.pdf
e. Applicant's Clinical Trial Protocol, version 1, available at: \\cdsesub1\evsprod\ind124943\0003\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\cel-hi-200\cel-hi-200-protocol-2017mar02.pdf
f. FDA Study May Proceed Letter, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8043f283&_afrRedirect=67769641363912
g. Applicant's Clinical Trial Protocol, available at: \\cdsesub1\evsprod\ind124943\0005\m1\us\proprietary-name-myxredlin-initial-request.pdf
h. FDA Proprietary Name Request Granted Letter, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8046920b&_afrRedirect=67623496558140
i. Applicant's Clinical Trial Protocol, version 2, available at: \\cdsesub1\evsprod\ind124943\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\cel-hi-200\cel-hi-200-protocol-amend-1-2017apr27.pdf
j. Applicant's Clinical Trial Protocol, version 3, available at: \\cdsesub1\evsprod\ind124943\0007\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\cel-hi-200\cel-hi-200-protocol-amend-2-2017jun02.pdf
k. Applicant's Original NDA Submission, available at: \\cdsesub1\evsprod\nda208157\0000\m1\us\cover-letter-2018apr26.pdf
l. FDA Acknowledgement – User Fees Received, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8049823b&_afrRedirect=585281644270479
m. FDA Refusal to File Letter, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804a49e4&_afrRedirect=585654576487354

n. Pharmacology/Toxicology Memorandum to File, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804a6df8&_afrRedirect=589207001119083
o. Applicant's Type A Meeting Request and Briefing Package, available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804b176e&_afrRedirect=590116698688688
p. Applicant's Resubmission After Refuse to File, available at: \\cdsesub1\evsprod\nda208157\0004\m1\us\cover-letter-2018aug22.pdf

Abbreviations: FDA, Food and Drug Administration; GLP, Good Laboratory Practice; IND, Investigational New Drug; iPSP, initial Pediatric Study Plan; L, liter; NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act; PIND, Pre-IND; PK, pharmacokinetic; PPQ, process performance qualification; PREA, Pediatric Research Equity Act; and TK, toxicokinetic.

3. Product Information and Rationale for Product Development

MYXREDLIN is a premixed, ready-to-use formulation of regular human insulin in an isotonic solution for intravenous use, with a proposed indication to improve glycemic control in adults and children with diabetes mellitus. The regular human insulin in this product is structurally identical to native human insulin, and is produced by recombinant DNA technology, utilizing *Pichia pastoris* (a yeast) as the production organism. MYXREDLIN will be provided as a clear, isotonic, aqueous, and colorless solution (target pH of (b) (4), range 6.5-7.2) containing 100 units of regular human insulin/100 mL of 0.9% sodium chloride and packaged in a 100 mL GALAXY bag. The Applicant claims that this product is intended to "provide convenience in the hospital setting while mitigating handling and dosing errors". MYXREDLIN is a short-acting insulin which is administered by IV infusion. In comparison to subcutaneously (SC) administered insulin which achieves peak insulin concentrations within 1.5 and 2.5 hours post dose, serum insulin concentrations increase rapidly with IV administration, and the median half-life is 49 minutes (23.4 minutes corrected for C-peptide) following discontinuation of the infusion.

Similar to the listed drug (NOVOLIN R), the regular human insulin in this product is a two-chain polypeptide hormone consisting of 51 amino acids (i.e., an A-chain composed of 21 amino acids and the B-chain composed of 30 amino acids). However, Novolin R is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Additionally, NOVOLIN R is available at a concentration of 100 units/mL in 10 mL glass vials and can be diluted to concentrations ranging from 0.05 to 1 unit /mL with 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride in polypropylene infusion bags for intravenous administration.[32]

Table 2: Comparison of MYXREDLIN and NOVOLIN R

Applicant	Novo Nordisk's NOVOLIN® R (Regular, Human Insulin Injection [recombinant DNA origin] USP) Listed Drug	Celerity's MYXREDLIN (Regular Human Insulin in 0.9% Sodium Chloride Injection) Proposed Drug
Product	NOVOLIN® R is a sterile human insulin injectable solution stored in 10 mL glass vials	Regular Human Insulin in 0.9% Sodium Chloride Injection is a sterile premixed human insulin injectable solution stored in a 100 mL GALAXY plastic bag
Active Ingredient	Human Insulin, USP	Human Insulin, USP
Host Cell Expression System	*Saccharomyces cerevisiae* (baker's yeast)	*Pichia pastoris* (yeast)
Total Drug Content	1000 U (100 U/mL in 10 mL glass vial)	100 U (1 U/mL in a 100 mL plastic bag)
Container Closure	Multi-use glass vial. When administered intravenously, polypropylene infusion bags should be used.	Single-use plastic container (GALAXY PL 2501)
Tonicity Agent	Can be used with the following infusion fluids: 0.9% Sodium Chloride, 5% Dextrose, or 10% Dextrose with 40 mmol/L Potassium Chloride	Premixed with 0.9% w/v Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)
Other Inactive Ingredients	Zinc Chloride approximately 70 mcg/10 mL (approximately 7 mcg/mL) Glycerol 160 mg/10 mL (16 mg/mL) Metacresol 30 mg/10 mL (3 mg/mL) pH adjusted with Sodium Hydroxide and/or Hydrochloric Acid Water for Injection, USP	Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)-also listed as a tonicity agent Monobasic Sodium Phosphate, Monohydrate, USP 29.0 mg/100 mL (0.290 mg/mL)* Dibasic Sodium Phosphate, Anhydrous, USP 41.2 mg/100 mL (0.412 mg/mL)* Water for Injection, USP
Volume	10 mL glass vial	100 mL GALAXY plastic container
Concentration	100 U/mL	1 U/mL
Dosage Form	Injectable; sterile solution (should be used in infusion systems using polypropylene infusion bags)	Injectable; sterile solution (premixed for intravenous infusion)

Applicant	Novo Nordisk's NOVOLIN® R (Regular, Human Insulin Injection [recombinant DNA origin] USP) Listed Drug	Celerity's MYXREDLIN (Regular Human Insulin in 0.9% Sodium Chloride Injection) Proposed Drug
Route of Administration	Injection: IV infusion or subcutaneous	Injection: IV infusion
Dosing Regimen (IV)	Total daily insulin requirements vary and are usually between 0.5 and 1.0 units/kg/day. Novolin® R can be used with the following infusion fluids: 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride.	Total daily insulin requirements vary and are usually between 0.5 and 1.0 units/kg/day.
Marketing Status	OTC	Prescription (Rx)

Source: Adapted from the Applicant's 2.2 Introduction to CTD, labeled as Table 1, page 4 of 7, available at: \\cdsesub1\evsprod\nda208157\0000\m2\22-intro\introduction-208157-us.pdf

* Monobasic sodium phosphate and monohydrate and dibasic sodium phosphate, anhydrous are added as buffers (pH range is 6.5-7.2, with a target pH of (b) (4).

In their rationale for why this product was developed, the Applicant notes that insulin is considered a High-Alert Medication by the Institute for Safe Medication Practices due to potential harm to patients from errors in dosing.[33] Celerity believes that their ready-to-use formulation may mitigate the dosing and handling errors associated with the more concentrated insulin solutions (e.g., U100 or U500), which must be diluted prior to administration. They note that the 1 unit/mL concentration is not currently available but is indicated for IV use after suitable admixture.

Besides the information provided by the Applicant, I also reviewed the medical literature related to potential medication errors associated with intravenous therapy. The rates of medication errors in intravenous drug preparation and administration in hospitals within individual countries have ranged from 3.3-97.7%.[34-50] Based on data from a national medication error-reporting program, 73,769 intravenous-related medication administration errors in pediatric patients were reported during a 5-year period, of which 6.8% of errors were due to the drug being prepared incorrectly.[51] Often these errors are due to improper concentration and mistakes in calculations. Additionally, in an audit of the preparation and administration of intravenous drugs at six hospital departments in the United Kingdom, France and Germany, the wrong diluent was used in in 1%, 18%, and 49% of cases, respectively, while at least one deviation in aseptic technique was observed among 100%, 58% and 19% of cases in the three countries.[52]

I concur that there is potential benefit in having a premixed insulin formulation intended for IV administration in healthcare facilities, especially in the acute care setting.

4. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted data from Study CEL-HI-200, randomized, crossover a euglycemic clamp study conducted in 58 healthy adult male volunteers (ages 19-50 years) to test for bioequivalence between MYXREDLIN and NOVOLIN R (diluted to 1 unit/mL prior to administration). Subjects randomly received an intravenous infusion of insulin at a rate of 1 mU/kg/min for six hours (i.e., 0.36 units/kg total dose) with an eight-hour blood sampling period on two separate occasions separated by a 7-10 day washout period (i.e., administered MYXREDLIN or NOVOLIN R and then the alternate product on the second visit). The blood glucose concentration was clamped at a target concentration of 9 mg/dL below the participant's fasting blood glucose (FBG) concentration. During the MYXREDLIN infusion, the average onset of action, defined as start of intravenous glucose infusion during the clamp, was observed at approximately 21 minutes after starting of the infusion, and the glucose infusion rate gradually increased to a maximum response rate of 13.7 mg/kg/min after five hours. Average insulin concentrations of about 300 pg/mL were attained between 1.5 to 6 hours after starting the infusion and returned to baseline concentrations by 1.5 hours after discontinuing the infusion. The mean terminal half-life was estimated to be 23.4 minutes.

The prespecified bioequivalence (BE) criteria (i.e., 90% confidence interval [CI] of 0.8 to 1.25 for the MYXREDLIN/NOVOLIN R least square (LS) geometric mean ratio [GMR]) $AUC_{INS\text{-}SS\ 300\text{-}360min}$ (GMR 1.0; 90% CI 0.96, 1.03) was met. The C-peptide-adjusted human insulin concentrations (reflective of endogenous insulin change during the clamp procedure) also were consistent between treatment arms. The 90% CIs for the LS GMR of the primary PD endpoint ($AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$) were within the prespecified BE bounds, (i.e., 1.0; 90% CI 0.96, 1.04).

The clinical pharmacology reviewer for this Application, Dr. Tao Liu, felt that the primary PK and PD endpoints were similar between the two products, and therefore, the Office of Clinical Pharmacology (OCP) found the Application approvable from a clinical pharmacology perspective. I concur with this assessment. For a detailed discussion of this study, please refer to the Clinical Pharmacology Review by Dr. Liu (dated May 15, 2019).

Additionally, Dr. Li-Hong Yeh, from the Office of Study Integrity and Surveillance (OSIS), conducted the surveillance inspection of the analytical portion of Trial CEL-HI-200 (i.e., Studies CA19891-01 and CA19891-02 for determination of human insulin and C-peptide, respectively) performed at (b) (4) . Based on his review of inspectional findings (e.g., study records, facilities, laboratory equipment, method validation, sample analyses, and interviews with the site's management and staff), he felt that the analytical data from the audited studies were reliable to support a regulatory decision. The final inspection classification was No Action Indicated (NAI). Please refer to Dr. Yeh's review (dated February 22, 2019) for additional information.

5. Chemistry, Manufacturing and Controls (CMC) and Clinical Microbiology

The Quality Review for this Application was performed by Drs. William Hallett (Application Team Lead), Anika Lalmansingh (Regulatory Business Process Manager), Anjali Shukla (Drug Substance/Product), Scott Dallas (Labeling), Laurie Nelson and Peter Qiu (Facility), Scott Nichols and Patricia Hughes (Microbiology – Drug Substance), and Virginia Carroll and Reyes Candau-Chacon (Microbiology – Drug Product). In his review (dated May 28, 2019), Dr. Hallett noted that the manufacturing of regular human insulin is well controlled, yielding a consistently high-quality product, and that the conditions used in manufacturing were sufficiently validated. For further discussion of the quality assessment of this Application please refer to his review.

A pre-approval inspection of the drug substance manufacturing facility ((b) (4) was conducted from (b) (4). The inspection covered the quality, production, facilities and equipment, materials, packaging and labeling, and laboratory control systems. A six-item FDA Form 483 was issued for the following deficiencies:

- Discrepancies between the information submitted in Drug Master File (DMF) (b) (4) and the human insulin manufacturing process performed at (b) (4)
- The firm's bacterial endotoxin test (Gel-Clot method) for Human Insulin (rDNA) finished product (API) is deficient.
- The environmental monitoring of clean rooms by microbiological methods is deficient.
- Laboratory controls failed to ensure that the Empower chromatographic system software appropriately reports the quality characteristics of the drug product.
- The quality unit failed to ensure that a critical process deviation was documented and investigated.
- The quality unit failed to ensure that effective systems are used for calibrating critical equipment.

The facility was classified as Voluntary Action Indicated (VAI). Overall, the firm was considered acceptable, and the drug substance manufacturing and testing sites were inspected and found to be compliant.

In the review of the microbial control and microbiology product quality of drug substance (i.e., recombinant human insulin expressed in *Pichia pastoris*), Dr. Nichols concluded that the drug substance portion of the Application was adequate and recommended approval. However, he recommended a single postmarketing commitment (PMC) requiring the Applicant to submit a supplement cross-referencing an updated DMF with established action limits for bioburden and endotoxin, and with the bioburden and endotoxin method qualification for the associated process steps (please refer to PMC #1 below).

The bioburden method qualification of drug product was originally performed by (b) (4) (b) (4) using a single lot of drug product. However, at the request of the Agency

(dated April 18, 2019), the Applicant agreed to provide the results of a bioburden method qualification study with three lots of drug product at the routine testing site (i.e., (b) (4) (b) (4) in accordance with United States Pharmacopeia (USP) <61>. These data were submitted on May 21, 2019, and acceptance criteria (i.e., the mean inoculum count < (b) (4) colony-forming unit [CFU] and mean percent recovery compared to controls between (b) (4) %) were met for all samples. In her review (dated April 30, 2019/Addendum May 22, 2019), Dr. Carroll stated that from a sterility assurance and quality microbiology perspective the Application is approvable, and that no inspection follow-up items were identified.

Overall, OPQ felt that the data submitted in this Application were adequate to support the conclusion that the manufacture of MYXREDLIN is well-controlled and leads to a product that is pure and potent, and recommended approval for human use under conditions specified in proposed product labeling. They will recommend the following PMC:

1. (b) (6)

I concur with OPQ's quality assessment of this Application.

6. Nonclinical Pharmacology/Toxicology

To establish a scientific bridge between MYXREDLIN and NOVOLIN R, the Applicant conducted *in vitro* functional assays comparing the activity (e.g., binding affinity of insulin and insulin growth factor-1 [IGF-1], and metabolic and mitogenic activity) between these products. The impurity profile of MYXREDLIN also was qualified in a two-week repeat-dose rat toxicity study ("bridging study" to qualify the safety of excess [(b) (4) impurities).

The Pharmacology/Toxicology reviewer for this Application, Dr. Parvaneh Espandiari, recommended approval of this Application. In her review, she noted that the toxicologic profile of recombinant human insulin is well established, and that hypoglycemia (the dose-limiting toxicity finding in animals) is a relatively insensitive endpoint for comparing these insulin products. Therefore, she felt that *in vitro* assessments were more sensitive for evaluating comparability. Based on her review of the Applicant's nonclinical findings, Dr. Espandiari concluded that the *in vitro* functional assays did not indicate meaningful differences between MYXREDLIN and NOVOLIN R, and that the two-week toxicology study did not show any safety issues related to (b) (4) impurities (i.e., (b) (4) and (b) (4)). Please refer to the Pharmacology/Toxicology Review (dated April 29, 2019) provided by Dr. Espandiari for additional information related to the MYXREDLIN nonclinical program.

I concur that the nonclinical findings from this Application support approval.

7. Efficacy

Besides the single Phase 1 clinical study (CEL-HI-200), no efficacy trials were conducted to support this NDA. Thus, there is no statistical review for this Application.

8. Safety

The only clinical data submitted to support this NDA were limited to the single Phase 1 clinical pharmacology study (CEL-HI-200) in healthy volunteers (i.e., no additional clinical trials and safety data were submitted). As CEL-HI-200 was a randomized, crossover, euglycemic glucose clamp study intended to demonstrate bioequivalence between MYXREDLIN and NOVOLIN R, all subjects were only exposed to a single six-hour infusion of MYXREDLIN. Therefore, these data do not inform a substantial safety assessment. However, the safety of MYXREDLIN is expected to be similar to the listed drug (NOVOLIN R).

In Study CEL-HI-200, there were no deaths or serious adverse events (SAEs). However, one subject withdrew due to AEs (Subject (b) (6) who presented with intermittent junctional rhythm prior to dosing in the second treatment period). Treatment-emergent adverse events (TEAEs) were reported for 10 (17.2%) subjects, of which five occurred following the MYXREDLIN infusion (i.e., 'Ear discomfort'; 'Infusion site extravasation'; 'Closed globe injury'; 'Electrocardiogram abnormal'; and 'Ecchymosis'). All TEAEs were reported as mild in intensity. Two subjects had abnormal, clinically meaningful 12-lead electrocardiogram (ECG) changes (Subjects (b) (6) and (b) (6)). These cases are discussed below.

Subject Narratives — Electrocardiogram Findings:

Subject (b) (6) a 25-year-old Caucasian male had a 12-lead ECG prior to dosing in Treatment Period 2 which showed an intermittent junctional rhythm alternating with a normal sinus rhythm, interpreted by the investigator as abnormal and clinically significant. The event occurred approximately 11 days following a single six-hour infusion of MYXREDLIN (29.4 units total dose). At the time of the event, the subject was asymptomatic with normal vital signs. He had no relevant past medical history and did not receive any concomitant medications during the study. Following review of the source documentation, it was noted that the screening ECG prior to administration of investigational product (IP) also showed an intermittent junctional rhythm. The AE was classified as mild, and the investigator felt that the observed ECG finding was not related to IP. However, due to a possible safety concern, the subject was not dosed with NOVOLIN R and was discontinued from the study by the investigator. The subject was advised to follow-up with his primary care provider. The subject's ECG at follow up approximately four weeks following the event was again abnormal but interpreted as not clinically significant.

Based on similar ECG findings at screening and prior to administration of IP at Treatment Period 2 (i.e., 11 days after receiving Myxredlin; median half-life of 23.4 minutes), I concur that the abnormal ECG findings were not related to IP.

Subject (b) (6)**:** a 32-year-old Caucasian male had ECG findings suggestive of Brugada syndrome approximately 2.5 hours after a six-hour infusion of MYXREDLIN 23.4 units in Treatment Period 2. The subject was asymptomatic at that time and his physical examination and vital signs were unremarkable. The AE was classified by the investigator as mild. The subject previously experienced a vasovagal episode (reported as mild by the investigator) upon placement of the IV line prior to administration of NOVOLIN R in Treatment Period 1. He denied a family history of cardiac issues, sudden arrhythmias, or sudden death. He had no relevant past medical history, did not receive any concomitant medications during the study, and his clinical laboratory results were not informative. Given the syncopal episode during IV placement in Treatment Period 1 and abnormal ECG findings in Treatment Period 2, the subject was transported to a local emergency room (ER) for further evaluation. The ECG performed in the ER was interpreted as not clinically significant. The investigator felt that the abnormal ECG possibly associated with Brugada syndrome was not related to IP.

Brugada syndrome is an autosomal dominant genetic disorder characterized by abnormal ECG findings and an increased risk of ventricular tachyarrhythmias and sudden cardiac death.[53] Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1 to V2, although isolated cases presenting with similar findings involving the inferior ECG leads also have been observed.[54-57] Patients with these ECG findings who experience sustained ventricular tachycardia or sudden cardiac death or have other associated clinical criteria (e.g., syncope, atrial fibrillation, nocturnal agonal respiration) are considered to have Brugada syndrome. Asymptomatic patients with the ECG features but without other clinical criteria are considered to have the Brugada pattern. In some patients with the Brugada pattern, the ECG changes may be transient or variable over time. Subject (b) (6) appeared to have the Brugada pattern. The prevalence of an asymptomatic Brugada ECG pattern is reported to be between 0.1-1% depending upon the population studied.[57-64] Review of the medical literature identified several reports in which intravenous infusions of glucose with/without insulin unmasked (i.e., accentuated) the ST segment elevation of Brugada syndrome.[65-67]

Although I concur that a causal association of MYXREDLIN and the abnormal ECG findings cannot be established or completely ruled out, it is possible that infusions of insulin and glucose may have unmasked the Brugada ECG pattern observed in this subject. Additionally, susceptibility to vasovagal syncope in this subject (i.e., the syncopal episode reported with IV placement in Treatment Period 1) also may be suggestive of autonomic dysfunction associated with Brugada pattern/syndrome.[68-70]

Applicant's Rational for Not Conducting Immunogenicity Assessments

Blood samples for assessments of anti-insulin antibodies (AIAs), collected at the screening visit, prior to each infusion period, and at the follow-up visit, were stored for future analysis. Therefore, these data were not provided. In the Written Response to the Pre-IND meeting (PIND 124943, dated May 22, 2015) the Agency offered the Applicant the opportunity to provide justification for why immunogenicity assessments would not be necessary with

MYXREDLIN.[2] The Applicant has provided this justification in their Clinical Overview,[3] which primarily included the following reasons:

A. Use of the same insulin drug substance from (b) (4) as is used in (b) (4) (i.e., the Applicant notes the drug substance for MYXREDLIN is the same as (b) (4)).
B. Use of compendial excipients with low immunogenic potential/concern.
C. An impurity profile that is similar to NOVOLIN R, with low immunogenic concern.
D. Low host cell impurities, microbial impurities, and amounts of aggregates (i.e., high molecular weight proteins [HMWP]), which reduce the risk for immunostimulation.
E. Demonstration of physicochemical and functional similarity between MYXREDLIN and NOVOLIN R.
F. Lower immunogenic potential associated with the administration of a single continuous IV infusion compared to repeat SC injections.
G. The proposed dilute formulation of 1 unit/mL of human insulin in isotonic 0.9% sodium chloride minimizes the potential for aggregation, compared to a high concentrated insulin formulation (e.g., 100 units/mL).

The structure of the drug substance in MYXREDLIN is identical to native human insulin. The Applicant noted that based on structural characteristics (e.g., primary, secondary and tertiary structures of insulin manufactured at (b) (4)), functional activity (e.g., insulin receptor binding, mitogenic potential, glucose uptake, and IGF-1 receptor binding) and the process-related impurity assessment (e.g., host cell impurities, microbial impurities, and aggregates), the immunogenic profile of MYXREDLIN is expected to be similar to the listed drug.

Semisynthetic and recombinant human insulins are immunogenic, with the development of insulin antibodies reported in 5-98% of patients treated with these products.[71-76] Although there is some concern that high levels of insulin antibodies may be associated with dysglycemia (e.g., hypoglycemia, hyperglycemia or insulin resistance)[77-79] or hypersensitivity,[80-82] there is limited evidence that anti-insulin antibody development is associated with clinically meaningful metabolic instability or local/systemic allergic reactions.[83-85] Typically, hypoglycemia associated with insulin is due to excessive insulin doses, exercise or missed meals/snacks, while poor metabolic control is often related to inadequate insulin (e.g., missed doses), mistimed insulin administration, excess caloric intake, and/or inadequate exercise.[86] Additionally, the incidence of hypersensitivity reactions with recombinant human insulins is relatively rare (reported in <1% to 2.4% of patients),[87,88] and these reactions are often attributed to additives/excipients of the product or container (e.g., stabilizers [zinc and protamine][89-93] preservatives [paraben, meta-cresol, phenol and isophane],[94] and/or latex[95]).[80,81,87,88,96-99]

[2] Applicant's Pre-IND Meeting Responses (PIND 124943, dated March 31, 2015), page 10 of 20, available at: \\cdsesub1\evsprod\nda208157\0000\m1\us\correspondence-pre-ind.pdf
[3] Applicant's Clinical Overview, pages 6-12 of 15, available at: \\cdsesub1\evsprod\nda208157\0000\m2\25-clin-over\clinical-overview-208157-us.pdf

Based on the above justification, approval by the Pharmacology/Toxicology and OPQ review teams, and review of the medical literature, I believe that the Applicant's justification for not conducting immunogenicity assessments for a product intended to be administered intravenously as a single continuous infusion is reasonable. Further, I feel that conducting immunogenicity assessments for MYXREDLIN for the intended use would be impracticable.

9. Advisory Committee Meeting

No Advisory Committee meeting was held to discuss this product.

10. Pediatrics

No data regarding the use of this product in pediatric patients was included in the Application. On December 11, 2015, the Applicant submitted the initial Pediatric Study Plan (iPSP) for IND 124943 requesting exemption from the Pediatric Research Equity Act (PREA) requirements (i.e., a waiver of pediatric assessments).[4] In the Written Response (dated February 4, 2016) related to this iPSP, the Agency determined the Application does not consist of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and therefore would not trigger PREA.[5]

11. Financial Disclosure

The Applicant submitted a Form FDA 3454 for the single covered clinical study (CEL-HI-200), certifying they have not entered into a financial arrangement with any of the six clinical investigators participating in this study.

12. Labeling

At the time of this review, labeling negotiations were ongoing. The proposed labeling for MYXREDLIN is similar to the labeling of the listed drug (NOVOLIN R), but with removal of most of the language related to SC administration and admixture recommendations for IV infusion.

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[4] Applicant's Pediatric Study Plan, page 2 of 7, available at: \\cdsesub1\evsprod\ind124943\0001\m1\us\pediatric-study-plan.pdf

[5] Applicant's Other Correspondence Regarding Pediatric Exclusivity or Study Plans, page 2 of 7, available at: \\cdsesub1\evsprod\nda208157\0000\m1\us\other-corresp-regarding-pediatric-exclusivity-study-plans.pdf

13. Other Relevant Regulatory Issues

Besides the additional PMC requested by OPQ, no other relevant regulatory issues are pending at the time of this memorandum.

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