CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208157Orig1s000

SUMMARY REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	June 10, 2019
From	Patrick Archdeacon, MD Acting Clinical Team Lead Division of Metabolism and Endocrinology Products
NDA # / Sequence #:	NDA 208157
Applicant	Celerity
Date of Submission Receipt	August 22, 2018
PDUFA Goal Date	June 22, 2019
Proprietary Name / Established (USAN) names	MYXREDLIN/regular human insulin in 0.9% sodium chloride injection
Dosage forms / Strength	100 Units/ 100 mL intravenous infusion
Recommended Action	Approval
Recommended Indication(s)/Populations(s)	To improve glycemic control in adults and children with diabetes mellitus

1. Introduction

Myxredlin (regular human insulin in 0.9% sodium chloride injection) is a premixed, ready-to-use formulation of regular human insulin intended for IV administration in hospital or emergency room settings. The proposed indication for Myxredlin is to improve glycemic control in adults and children with diabetes mellitus. Celerity (hereafter referred to as the Applicant) has submitted a 505(b)(2) application that relies, in part, on the FDA's finding of safety and effectiveness for the listed drug Novolin R (regular human insulin injection; NDA 019938). Whereas the listed drug relied upon is produced by recombinant DNA technology in *Saccharomyces cerevisiae* and is available at a concentration of 100 U/mL in a 10 mL glass vial, Myxredlin is produced by recombinant DNA technology in *Pichia pastoris* and is intended to be marketed at a concentration of 1 U/mL in a 100 mL plastic bag. The Applicant proposes that a premixed, ready-to-use formulation will reduce medication errors associated with IV use of insulin, which requires dilution prior to administration with currently marketed insulin solutions.

As described in this memo, I concur with the recommendations of the various review disciplines to approve NDA 208157.

This memo references the following documents/sources:

Subject	Author	Date
Clinical	Frank Pucino	June 7, 2019
Office of Biotechnology Products	Anjali Shukla, Scott Dallas, Laurie Nelson, Peter Qiu, Scott Nichols, Patricia Hughes, Virginia Carroll, Reyes Candau-Chacon, William Hallett	May 28, 2019
Pharmacology/Toxicology	Parvaneh Espandiari	April 29, 2019
Clinical Pharmacology	Tau Liu	May 15, 2019
Office of Prescription Drug Promotion (OPDP)	Ankur Kalola	May 28, 2019
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane Conrad	May 17, 2019
Office of Study Integrity and Surveillance (OSIS)	Li-Hong Yeh, Kara Schreiber	February 21, 2019
Office of Study Integrity and Surveillance (OSIS)	Sripal Reddy	May 8, 2019

2. Background

Myxredlin (regular human insulin in 0.9% sodium chloride injection) is a premixed, ready-to-use formulation of regular human insulin intended for IV administration in hospital or emergency room settings. The proposed indication for Myxredlin is to improve glycemic control in adults and children with diabetes mellitus. Celerity (hereafter referred to as the Applicant) has submitted a 505(b)(2) application that relies, in part, on the FDA's finding of safety and effectiveness for the listed drug Novolin R (regular human insulin).

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. Patients with type 1 diabetes mellitus (T1D) have experienced autoimmune destruction of the pancreatic β cells responsible and therefore have no endogenous insulin production or secretion; patients with type 2 diabetes mellitus (T2D) have developed β cell dysfunction and insulin resistance. Patients with T1D have an absolute requirement for exogenous insulin replacement to maintain glycemic control. Glycemic control in patients with T2D may also improve with exogenous insulin administration.

Patients with both T1D and T2D routinely self-administer insulin subcutaneously, using syringes, insulin pens, or insulin pumps. The insulin products self-administered by patients are available at concentrations of 100 U/mL or higher (e.g., 500 U/mL). Rarely, in the setting of critical illnesses [including but not limited to events of diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS)] or surgery, glycemic control of diabetic patients is achieved through the highly monitored and carefully titrated IV administration of insulin. Currently marketed insulin products are indicated for IV use, but first require admixture with appropriate volumes of infusion fluids prior to IV administration. The need for dilution with infusion fluids introduces a potential for medical errors with IV use of insulin (see the Clinical Memo from Dr. Frank Pucino for extensive literature references documenting such errors, including errors related to dose calculation, diluent selection, and improper aseptic technique). The Applicant proposes that a ready-to-use 1 U/mL formulation of regular human insulin for administration in hospital and emergency room settings by health care professionals will mitigate dosing and handling errors associated with IV insulin use.

This 505(b)(2) application for Myxredlin includes bridging studies to provide a basis for relying on the Agency's finding of safety and effectiveness for the listed drug. The scientific bridge provided includes physico-chemical and biological testing to characterize the primary, secondary, and tertiary structures of the insulin molecule, as well as assessments of impurities, including (b) (4) and (b) (4). The bridging studies also included *in vivo* and *in vitro* evaluations of receptor affinity and biological activity. Finally, the Applicant conducted a two-week bridging toxicology study in rats. Please see the discussion in Sections 3 and 4 below for details.

For insulin products previously approved through the 505(b)(2) pathway, the Agency has required clinical trials to evaluate the potential impact of immunogenicity on effectiveness (based on measures of HbA1c) and safety (including evaluations of immune reactions and hypoglycemia). Because Myxredlin is intended for acute use only in the setting of a hospital or emergency room, immunogenicity risk is considered low and the endpoints used in such

clinical trials are not suitable for the evaluation of Myxredlin. The clinical evaluation of Myxredlin instead relied solely on a double-blind, randomized, crossover euglycemic clamp study (CEL-HI-200) to demonstrate the pharmacokinetic and pharmacodynamic comparative bioavailability of Myxredlin and the listed drug. This study design does not support an evaluation of the immunogenicity of Myxredlin, and the Applicant submitted a justification for not providing an immunogenicity assessment for Myxredlin. Please see the discussion in Sections 5, 6, and 7 below for details.

The Applicant had initially submitted the NDA for Myxredlin on April 26, 2018. The application was not initially accepted for filing due to non-payment of PDUFA user fees. On May 16, 2018, FDA informed the Applicant that the required fees had been accepted with the new Application receipt date of May 4, 2018. On July 2, 2018, FDA issued a Refuse to File letter due to 1) the lack of prospective validation results for three consecutive drug product lots produced at the commercial scale and 2) an insufficient bridging toxicity study. It was subsequently clarified that the Applicant had completed and submitted an adequate two-week bridging toxicity study. During an August 16, 2018 Type A meeting, FDA agreed to the Applicant's proposal to resubmit the Application using a (b) (4) commercial scale rather than the (b) (4) commercial scale. The Applicant resubmitted the NDA for Myxredlin on August 22, 2018. For additional details regarding the regulatory history of NDA 208157, please see the Clinical Memo by Dr. Frank Pucino.

3. CMC

The Office of Biotechnology Products (OBP) review team recommends approval of the NDA. The team concluded, and I concur, that the data submitted in the application support the conclusion that the manufacture of Myxredlin is well-controlled and leads to a product that is pure and potent. Please see the individual reviews of the OBP team members for additional details.

Myxredlin (regular human insulin) is a protein composed of two amino acid chains: the A-chain consists of 21 amino acids, the B-chain consists of 30 amino acids. Myxredlin is produced in a recombinant *Pichia pastoris* cell line. The final drug product comprises 100 U of regular human insulin formulated in sodium chloride (900 mg), monobasic sodium phosphate, monohydrate (29.0 mg), dibasic sodium phosphate, anhydrous (41.2 mg), and water for injection, USP (100 mL) in a 100 mL single-port PL2501 GALAXY bag. Appropriate compatibility studies were performed for the container closure system.

As described in the summary review from OPQ, the Applicant provided an analytical similarity assessment of Myredlin and Novolin R (the listed drug) comparing the following physico-chemical characteristics using multiple batches of product: primary, secondary, and tertiary structure; molecular size; isoelectric point; particle size; sub-visible particles; intact and reduced mass; aggregates; pH; visual appearance; Insulin Assay [% (b) (4), % (b) (4), other related substances]; HMWP; osmolality; purity; insulin receptor binding; mitogenic potential; glucose update; and IGF-1 receptor binding. The potency assay used is reversed-phase high

performance liquid chromatography (RP-HPLC) that measures the main peak of human insulin and [redacted], compared to a USP human insulin reference standard.

The human insulin API is manufactured a [redacted]. The Office of Biotechnology Products and the Division of Microbiology Assessment determined that [redacted] Drug Master File (DMF) [redacted] is adequate.

The OBP recommended (and I concur with) a single post-marketing commitment:

- [redacted]

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Parvaneh Espandiari, recommends approval of NDA 208157. I concur with her recommendation. Please see Dr. Espandiari's review for additional details.

To establish a scientific bridge between Myxredlin and Novolin R, the listed drug relied upon, the Applicant completed *in vitro* functional assays comparing the activities of the two insulins. Some of the assays required the extraction of insulin from Novolin R and reformulation in the Myxredlin injection buffer to avoid confounding the assays with some of the Novolin R excipients. Dr. Espandiari determined (and I concur) that this approach was appropriate. The assays evaluated insulin and IGF-1 receptor binding and activation, *in vitro* metabolism, and mitogenic activity. For the assays of insulin receptor binding, the Applicant tested only IR-B (the long-form receptor present in adult tissues) and not IR-A (the short-form receptor present in fetal tissues and some cancer cells). Dr. Espandiari concluded (and I concur) that the because Myxredlin is not intended for chronic use that binding affinity data for IR-A are not needed. The assays demonstrated that Myxredlin and Novolin R both bind and activate IR-B with similar affinity and that both bind the IGF-1 receptor with 1000-fold lower affinity compared to IR-B. Myxredlin and Novolin R also performed similarly in assays of *in vitro* metabolism (i.e., insulin mediated glucose update in 3T3 cells) and mitogenicity.

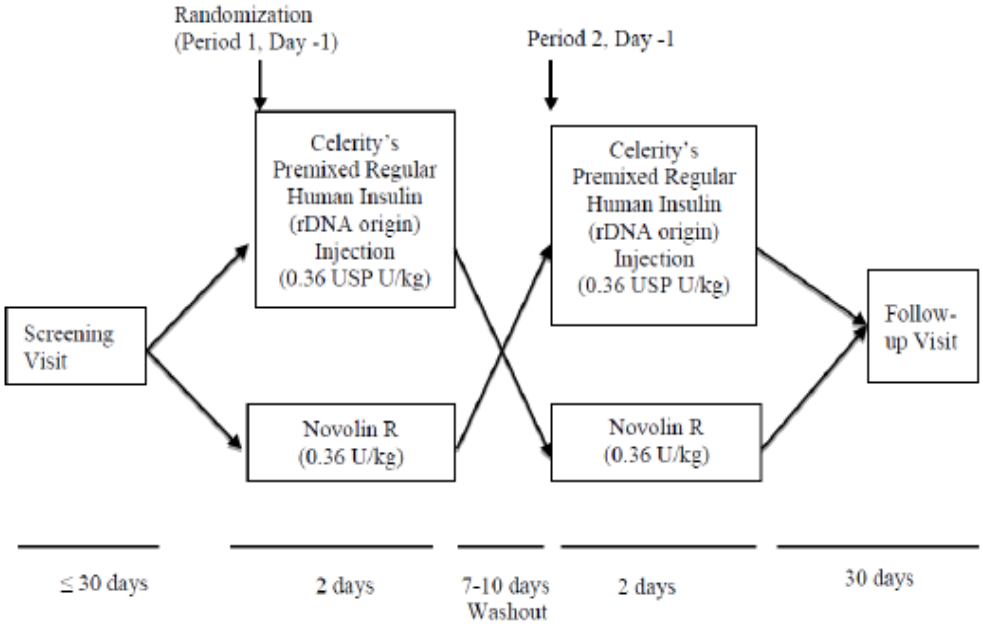
In addition, due to differences in the impurity profiles of Myxredlin and Novolin R (specifically with regards to the levels of [redacted] impurities), a two-week repeat-dose rat toxicity study with a two week recovery period was conducted. Dr. Espandiari concluded (and I concur) that the two-week toxicity study did not demonstrate any meaningful safety issues.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Tao Liu, the clinical pharmacology reviewer, recommends approval of NDA 208157. I concur with his recommendation. Please see Dr. Liu's review for additional details.

In support of the NDA, the Applicant conducted a double-blind, randomized, cross-over, euglycemic glucose clamp study (CEL-HI-200) to compare Myxredlin and Novolin R in 58 healthy male subjects. The study assessed and compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of Myxredlin and an equivalent dose of Novolin R when administered by IV infusion over 6 hours. The study design is shown below:

Figure 1: CEL-HI-200 Study Design

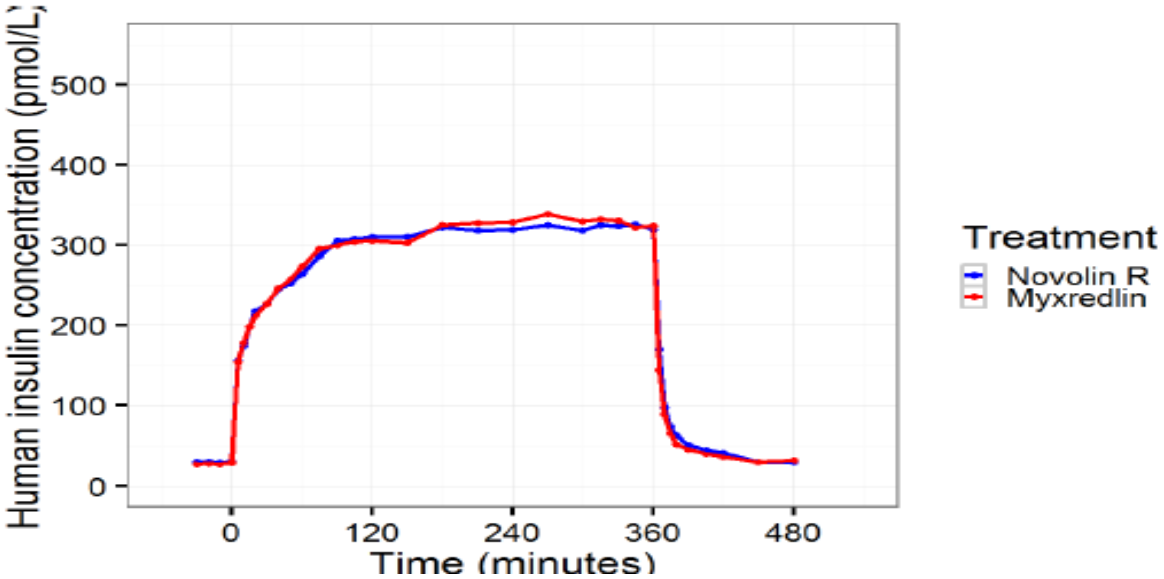


Source: CEL-HI-200 Clinical Study Report

Study subjects received 1.0 mU/kg/min for 6 hours of either Myxredlin or Novolin R, resulting in a total dose of 0.36 U/kg/trial. Following the start of the infusion, blood glucose concentration was clamped at a target 9 mg/dL below the subject's fasting blood glucose by IV infusion of 20% glucose.

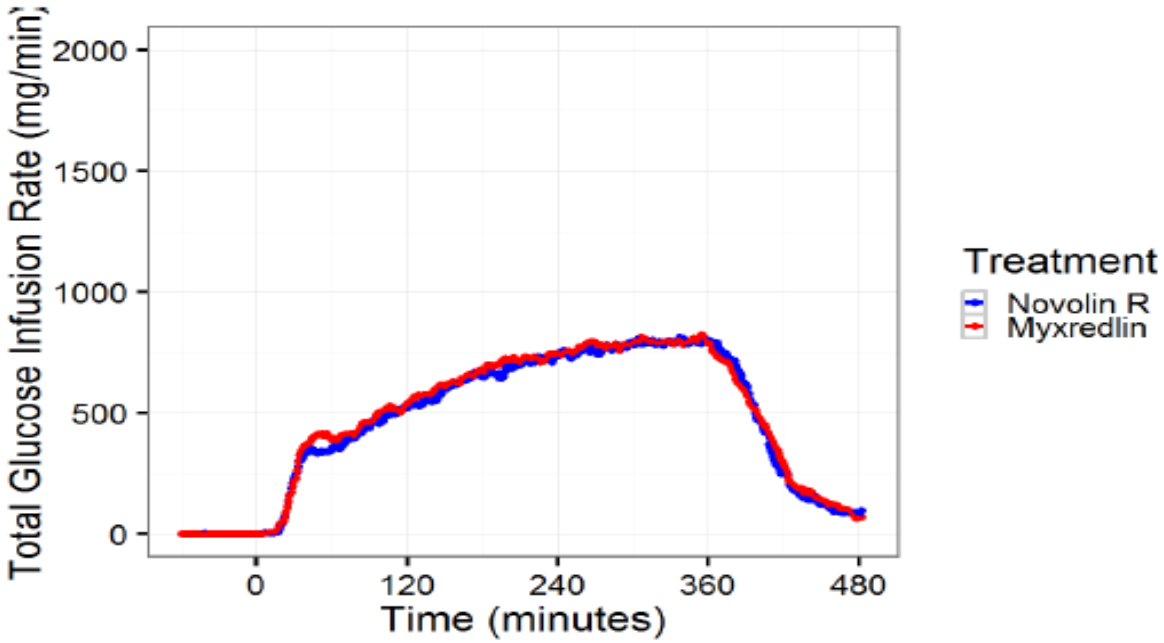
The insulin concentration profiles achieved were similar for the two treatment groups (see Figure 2): concentrations reached steady state at approximately 1.5 hours, remained stable until the end of the infusion, and returned to baseline at approximately 1.5 hours after the end of the infusion. The observed glucose infusion rates (GIR) were also similar for the two treatment groups (see Figure 3): GIR gradually increased from baseline, reached steady state at approximately 4.5 hours, and returned to baseline about 2 hours after the end of the insulin administration. Observed blood glucose concentrations during the clamp procedure were similar for the two treatment groups (see Figure 4). Statistical analyses also demonstrate the similarity of the PK and PD profiles (see Table 1 and Table 2): the PK and PD parameters met the pre-specified criteria for geometric mean ratios and 90% CIs (i.e., the parameters for Myxredlin and Novolin R were all within 80-125%). Dr. Liu concluded (and I concur) that these results support the scientific appropriateness of reliance on FDA's finding of safety and effectiveness for Novolin R to support approval of Myxredlin.

Figure 2: Insulin Pharmacokinetics by Treatment



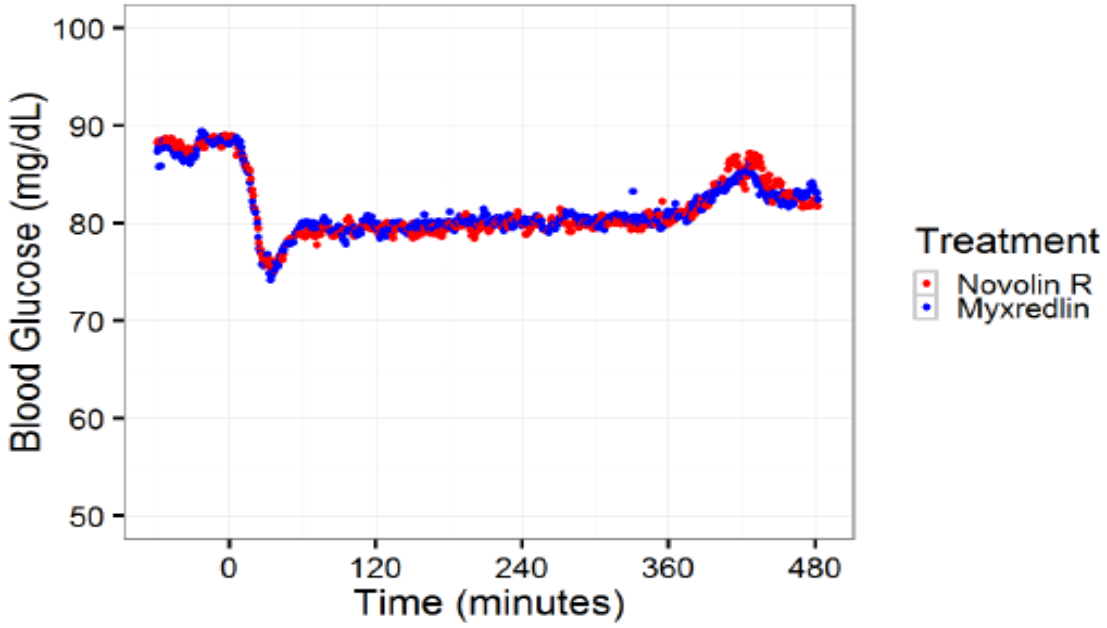
Source: FDA Clinical Pharmacology Review

Figure 3: Arithmetic Mean of GIR (mg/min) by Treatment



Source: FDA Clinical Pharmacology Review

Figure 4: Arithmetic Mean of Blood Glucose by Treatment



Source: FDA Clinical Pharmacology Review

Table 1: AUC insulin steady-state 300-360 min

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]
$AUC_{INS-ss\ 300-360\ min}$ (pM*min)	Geometric LS Mean (SE)[2]	19097.3 (514.34)	19266.5 (518.44)	1.0 (0.02)	0.96, 1.03
$AUC_{INS-ss\ 300-360\ min}$ (pM*min) (C-peptide corrected)	Geometric LS Mean (SE)[2]	18423.4 (493.99)	18585.5 (497.92)	1.0 (0.02)	0.96, 1.02

Source: CEL-HI-200 Clinical Study Report

Table 2: AUC GIR steady-state 300-360 min

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]	95% CI for Ratio[3]
$AUC_{GIR-ss\ 300-360\ min}$ (mg)	Geometric LS Mean (SE)[2]	46461.9 (1424.53)	46543.0 (1425.55)	1.0 (0.03)	0.96, 1.04	0.95, 1.05

Source: CEL-HI-200 Clinical Study Report

The Office of Study Integrity and Surveillance (OSIS) inspected both the study site and the analytical portion of clinical study CEL-HI-200. Ds. Sripal Reddy, Dr. Li-Hong Yeh, and Dr. Kara Schreiber concluded (and I concur) that the data from CEL-HI-200 are reliable to support a regulatory decision.

6. Clinical/Statistical- Efficacy

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The only clinical data submitted in support of NDA 208157 derived from CEL-HI-200 (the clinical pharmacology study described in section 5). For that reason, there is no statistical review for the application.

7. Safety

While this 505(b)(2) application relies primarily on FDA's finding of safety for Novolin R, Dr. Pucino evaluated the safety data that were collected in CEL-HI-200 (the clinical pharmacology study described in section 5). Overall, Dr, Pucino recommended (and I concur) approval of the NDA. Please see Dr. Pucino's review for additional details.

There were no deaths or serious adverse events (SAEs) observed in CEL-HI-200. Two subjects in the study were observed to have ECG changes. One subject was noted to have an intermittent junctional rhythm on ECG 11 days after exposure to Myxredlin; at follow-up four weeks later, the ECG remained abnormal but was interpreted as not clinically significant. Another subject had ECG findings "suggestive of Brugada syndrome" approximately 2.5 hours after the Myxredlin infusion; that subject was transported to a local emergency room for evaluation where an ECG was performed and interpreted as not clinically significant. While noting in his review that a causal association between Myxredlin and the abnormal ECG findings cannot be excluded, Dr. Pucino also notes that abnormal ECG findings in asymptomatic subjects are observed at a non-zero rate.

Immunogenicity of Myxredlin was not evaluated as part of CEL-HI-200. While blood samples for assessments of anti-insulin antibodies (AIAs) were collected at the screening visit, prior to each infusion period, and at the follow up visit, they were stored for future analysis only. The Applicant provided a justification in their Clinical Overview for not evaluating the immunogenicity of Myxredlin in clinical trials. Their arguments included: 1) the use of the identical drug substance (DS) in another product marketed outside of the US, 2) the low immunogenic potential of the compendial excipients, 3) the similarity of the impurity profile to the listed drug relied upon, 4) the low levels of host cell impurities, microbial impurities, and aggregates, 5) the physicochemical and functional similarity of Myxredlin to the listed drug relied upon, 6) the reduced potential for clinically relevant immunogenic responses with an insulin product intended for acute rather than chronic use, and 7) the reduced potential for clinically relevant immunogenic responses with a highly diluted (1 U/mL in 0.9% sodium chloride) insulin product. The Applicant also argued that the similarities in structural characteristics, functional activity, and process-related impurities support a conclusion that the immunogenic profile of Myxredlin can be expected to be similar to that of the listed drug relied upon. Dr. Pucino concluded (and I concur) that this justification, in conjunction with a review of the medical literature regarding the clinical impact of immunogenicity associated with exogenous administration of insulin, adequately addresses any clinical concerns related to immunogenicity for this insulin product that is intended for acute IV administration only.

8. 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.

9. Pediatrics

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). 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.

10. Labeling

The proposed labeling for Myxredlin is similar to the labeling for the listed drug relied upon. Ariane Conrad, the Division of Medication Error Prevention and Analysis (DMEPA) reviewer, provided recommendations to the Applicant for the carton and container labeling for Myxredlin. She concluded (and I concur) that the revised carton and container labeling are acceptable from a medication error perspective. Ankur Kalola, the Office of Prescription Drug Promotion (OPDP) reviewer, provided recommendations to the Applicant for the package insert. The proposed edits from OPDP and from DMEP removed language from the labeling relevant to outpatient and subcutaneous use of insulins. I concur with the recommendations from OPDP. In addition, Scott Dallas (the OBP reviewer) proposed edits to section 11 (Description) to adhere to best labeling practices and Tao Liu (the clinical pharmacology reviewer) proposed edits to section 12 (Clinical Pharmacology) to add data from CEL-HI-200. I concur with these recommendations.

Because Myxredlin is intended only for administration by health care professionals in hospital and emergency room settings, the labeling does not include a patient package insert.

11. Recommendations

I recommend approval of NDA 208157, Myxredlin (regular human insulin in 0.9% sodium chloride injection).

My recommendation is based both on Myxredlin-specific data and also, in part, on the finding of safety and effectiveness of the listed drug (Novolin R, NDA 019938).

The NDA included bridging studies to provide a basis for relying on the Agency's finding of safety and effectiveness for Novolin R. The studies include physico-chemical and biological testing to characterize the primary, secondary, and tertiary structures of the insulin molecule;

assessments of impurities, including (b) (4) and (b) (4); and *in vivo* and *in vitro* evaluations of receptor affinity and biological activity. Finally, the Applicant conducted a two-week bridging toxicology study in rats. I conclude that the scientific bridge comprised of those studies provide an adequate basis for relying, in part, on the Agency's finding of safety and effectiveness for Novolin R.

Myxredlin is a premixed, ready-to-use formulation of regular human insulin intended for IV administration in hospital or emergency room settings to achieve glycemic control in acutely ill patients with diabetes or in patients with diabetes undergoing surgery. This intended context of use precluded reliance on the usual study designs used for Phase 3 trials of insulin products intended for chronic outpatient use to improve glycemic control in patients with diabetes. While clinical evaluations of insulin products intended for chronic use generally include an assessment of glycemic control based on HbA1c responses over months, the Division concluded (and I concur) that such an assessment would not be relevant nor particularly informative for a product intended for short-time use during a hospitalization. The PD data obtained from the euglycemic clamp study, on the other hand, are very informative. The administration of Myxredlin in the clamp study accurately represents the time action profile of the product. For that reason, the demonstration of comparative bioavailability (in terms of both PK and PD parameters) in the clamp study constitutes additional compelling evidence of clinical effectiveness. Finally, I concur with the justification of the Applicant for not conducting a clinical assessment of immunogenicity for Myxredlin. Specifically, I agree that the similarities in structural characteristics, functional activity, and process-related impurities support a conclusion that the immunogenic profile of Myxredlin can be expected to be similar to that of the listed drug relied upon. Moreover, I agree that there is a significantly reduced potential for clinically relevant immunogenic responses with an insulin product intended for acute rather than chronic use.

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
06/19/2019 03:30:57 PM

LISA B YANOFF
06/19/2019 04:25:43 PM