CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208157Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208157

REFUSAL TO FILE

Celerity Pharmaceuticals, LLC
Attention: John Oberholtzer, J.D.
Senior Regulatory Affairs Manager
9450 Bryn Mawr Avenue Suite 640
Rosemont, IL 60018

Dear Mr. Oberholtzer:

Please refer to your New Drug Application (NDA) dated April 26, 2018, received May 4, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for human insulin (rDNA origin) injection 100 units/mL in 0.9% sodium chloride.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) 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. 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. For additional guidance please see ICH eCTD: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality-M4Q(R1) Quality Overall Summary of Module 2 Module 3: Quality, S.2.S.2.5 Process Validation and/or Evaluation.

2. In the Type B written responses for PIND 124943, dated May 22, 2015, we recommended that a GLP-compliant bridging toxicity study comparing your product with U.S.-approved Novolin R be conducted and submitted with your 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 your proposed product. (b) (4)

To avoid repeating the in vivo bridging toxicity study, we recommend you provide additional in vitro comparability studies with your to-be-marketed product and U.S.-approved Novolin R. In addition to studies already submitted, we recommend you provide comparisons of receptor binding affinity and receptor activation (autophosphorylation) for insulin receptor-A (IR-A) and receptor activation (autophosphorylation) for insulin receptor-B (IR-B).

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. Your application provides one year of drug product stability results for three (b) (4) scale registration lots. The drug product expiry will be determined during review of the NDA. The original application should contain at least 6 months of stability results for three lots of the validated commercial process as per ICH Q5C recommendations.

2. The drug product batch analysis and stability data provided included tabular summary data and Certificates of Analysis. To facilitate our review, provide high quality reproductions of representative raw data including chromatograms for all test methods used for release, stability, and characterization of the product in the NDA submission.

3. An interim alert limit of (b) (4) CFU/100 mL and an action limit of (b) (4) CFU/100 mL were proposed for pre-filtration bioburden sample and you have indicated that bioburden in-process limit will be established after (b) (4) data points. We recommend that you establish at a minimum a pre-sterile filtration bioburden limits of ≤ 10 CFU/100mL to be consistent with current industry practice.

4. Maximum hold time NMT (b) (4) hours at (b) (4) C was qualified for drug substance in (b) (4) using development batches. Any processing or hold times greater than (b) (4) hours should be validated for microbial control at commercial scale using (b) (4) runs. Bioburden samples should be taken at the beginning and end of the hold time prior to the subsequent (b) (4) step to demonstrate the microbial control.

5. On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

   Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, we noted that you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling.

Submit the following information on human insulin use in pregnant and lactating women with your resubmission:

a. A review and summary of all available published literature regarding human insulin,

b. A review and summary from your pharmacovigilance database,

c. Interim ongoing or final report on a closed pregnancy registry (if applicable),

d. Revised labeling, if appropriate, incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Additional Comments:

6. In the Type B written responses for PIND 124943, dated May 22, 2015, you were asked to provide a plan to assess product immunogenicity and determine whether it impacts the pharmacokinetics or clinical outcomes, or provide justification why immunogenicity assessments are not necessary for your product. We note that in your 'Clinical Overview' you provided justification for why immunogenicity assessments are not necessary for your product. Whether this justification will be adequate to support a 505(b)(2) application for your proposed insulin product will be a review issue.

7. As explained in FDA's Draft Guidance for Industry *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf (Transition Draft Guidance), an application for a protein product that has been submitted under section 505 of the FD&C Act and is pending on March 23, 2020, will not be approved. Accordingly, we recommend that sponsors of development programs for proposed protein products evaluate whether a planned submission under section 505 of the FD&C Act would allow adequate time for approval of the NDA prior to March 23, 2020, considering, among other things, whether the submission may require a second cycle of review and, for certain types of applications, whether unexpired patents or exclusivity may delay final approval. If a sponsor is unsure whether its proposed product may receive approval under the FD&C Act by March 23, 2020, the sponsor should consider submitting a

biologics license application (BLA) under the Public Health Service Act instead. Please refer to the Transition Draft Guidance for additional information and recommendations to sponsors.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Callie Cappel-Lynch Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/

WILLIAM H CHONG
07/02/2018