DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210660

**GENERAL ADVICE**

Exela Pharma Sciences, LLC
Attn: Aruna Koganti
Executive Director of Clinical and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Dr. Koganti:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for L-Cysteine Hydrochloride Injection, USP, 50 mg/mL.

We also refer to your May 23, 2017, submission, containing the first portion of your NDA rolling review and your July 26, 2017 response to an information request from Oumou Barry, MHA, MT, ASCP, Lieutenant Commander, US Public Health Service, Regulatory Business Process Manager, Office of Program and Regulatory Operations, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research.

We have reviewed the referenced material and have the following recommendations:

Based on our previous experience with small volume parenteral drug products used in TPN, we have determined that the aluminum dose delivered by your drug product, L-Cysteine Hydrochloride Injection, 0.5g/10mL, should be limited to ≤ 0.6 mcg/kg/day. To comply with this dose level, a limit of ≤ 145 mcg/L aluminum is needed. The limit of 145 mcg/L for aluminum concentration in your drug product is derived based on the maximum dose of total amino acid at 3.5 gram/kg/day with 40 mg/gram of amino acid of L-cysteine added. Current clinical recommendations for total amino acid doses range from 0.5 to 3.5 gram/kg/day, and 20 to 40 mg of L-cysteine is required for each gram of amino acid in the final TPN infusion solution.

You have indicated that you intend to change the primary container closure from the glass vials to plastic vials in an attempt to reduce and control the level of aluminum in the drug product at release and throughout the desired product shelf-life. We remind you that this change will require full assessment of the proposed container closure leachables/extractables as well as toxicological evaluation of the potential leachable compounds. See our recommendations for safety assessment of leachables/extractables in the meeting minutes for PIND 128489 dated December 23, 2015. Additionally, container closure integrity must be established during accelerated and long-term stability to ensure that it is capable of protecting the drug product from its external environment and maintaining the drug product sterility throughout the proposed product shelf-life.

The primary container closure information must include material description and specification for each component of the proposed container closure system, the DMF number for each component, and the letter of authorization for the review of each referenced DMF. Regardless of whether the new container closure components have been accepted by the Agency for use in approved drug products, a thorough safety assessment of leachables/extractables will be needed due to the extremely low pH range (1-2.5) for your product.

We strongly recommend that you maintain communication with the Agency CMC review team to keep us informed on your progress and evolving strategy to resolve the concern about aluminum levels in the drug product. In addition to the information provided in PIND 128489 meeting minutes about the safety assessment of leachables/extractables, the Division's nonclinical team can provide further guidance as needed, and respond to your questions in order to facilitate the completion of the required safety assessment.

If you have any questions, call Evangela Covert, Regulatory Project Manager, at (301) 796-4075.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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DONNA J GRIEBEL
08/04/2017