CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207131Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Balajee Shanmugam Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	207131
Applicant Name	Celerity Pharmaceuticals, LLC
Date of Submission	October 16, 2014
PDUFA Goal Date	August 16, 2015
Established (USAN) Name	Cefazolin Injection*
Dosage Forms / Strength	2 g/100 mL cefazolin and 4% dextrose in GALAXY plastic container for injection
Proposed Indications	Pre-operative prophylaxis
Recommended Action:	Approval

**No proprietary/trade name was proposed for the drug product*

1.0 Introduction

This 505 (b)(2) NDA submitted by Celerity Pharmaceuticals provides for a premixed, frozen iso-osmotic solution of 2 g/100 mL cefazolin and 4% dextrose in a GALAXY plastic container for intravenous use after thawing at room temperature or under refrigeration. The drug product (b) (4) pre-operative prophylaxis since the product will only be administered before surgery. Celerity Pharmaceuticals is relying on the findings of safety and efficacy for the 2 g Cefazolin for Injection, USP and Dextrose Injection, USP marketed by B. Braun Medical Inc. (B. Braun) under NDA 050779.

2.0 Background

Cefazolin is a first generation semi-synthetic cephalosporin belonging to the β-lactam class of antibacterial drugs. The drug acts by inhibiting bacterial cell wall synthesis specifically by binding to penicillin binding proteins and exhibits activity against both gram positive (*Staphylococcus aureus, Stahphylococcus epidermidis, Streptococcus agalactiae, Streptococcus pneumonia, and Streptococcus pyogenes)* and gram negative (*E. coli and Proteus mirabilis)* bacteria. The proposed drug product has the same drug substance, strength (b) (4) dosage form, route of administration as the listed drug. Celerity intends to maintain the same dosing regimen as B. Braun's listed drug approved under NDA 050779 in that the proposed drug product (2 g dose) will be used in its entirety (and not any fraction thereof) and will be infused over 30 minutes. (b) (4)

(b) (4) Hence the indication was revised to pre-operative prophylaxis.

Baxter has an Abbreviated New Drug Application (ANDA), No. 063002, for a premixed-frozen product in l g/50 mL (0.02 g/mL) strength and will serve as the contract manufacturer for Celerity. (b) (4) . The 100 mL GALAXY plastic container is approved for packaging for/with other currently marketed IV solutions.

The appropriate discipline reviewers have completed evaluation of their respective review portions. For detailed information, please refer to discipline specific reviews.

3.0 Product Quality

The Product Quality reviewer for this application is Chunchun Zhang, Ph.D. Vinayak Pawar, Ph.D. is the Product Quality Microbiology reviewer.

Cefazolin drug substance is manufactured by (b) (4) and all CMC information related to the drug substance is referenced to the Drug Master File (DMF) (b) (4). The DMF has been previously reviewed and found adequate.

The proposed drug product Cefazolin injection, USP 2g/100 mL is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution in Galaxy plastic container (PL2040). The formulation, manufacturing process and equipment of the current proposed drug product (b) (4) Baxter's marketed product, Cefazolin Injection USP 1g/50mL in Galaxy container. All excipients used in the manufacture of the drug product are compendial and meet the requirements of the current USP/NF. The proposed drug product specification includes tests for the following quality attributes: pH, identification, assay, impurities, osmolality, sterility, bacterial endotoxins particulate matter, and fill volume. The acceptance criteria proposed are noted to be justified adequately.

DMF (b) (4) referenced for the GALAXY bags was found adequate for its intended use. Furthermore, the proposed bag (b) (4) Baxter's currently marketed product (1 g/50 mL Cefazolin Injection, USP) container system. The drug product is manufactured at Baxter's facility in Illinois. An overall recommendation of "Acceptable" has been issued by the Office of Process & Facilities for all facilities involved in manufacture of the

drug substance and the drug product. Based on available stability data, OPQ recommends granting 24-month expiration period at -20°C with a thawed label statement of "30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)" when stored in GALAXY plastic container (PL 2040). Dr. Vinayak Pawar, Product Quality Microbiology reviewer also recommends approval of the NDA. All outstanding Product Quality issues have been resolved adequately and Dr. Zhang recommends approval of the NDA from Product Quality perspective.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Dr. Amy Ellis. As noted above Celerity relies on the Agency's findings for the 2 g Cefazolin for Injection, USP and Dextrose Injection, USP marketed by B. Braun Medical Inc. (B. Braun) under NDA 050779. Therefore, the Applicant did not conduct any additional nonclinical toxicology study. As noted by Dr. Ellis, the product does not appear to have any new impurities or that exceed the ICH threshold level as compared to the listed drug that will require additional testing/qualification. Dr. Ellis recommends approval of the NDA.

5.0 Biopharmaceutics

Biopharmaceutics, reviewed by Kelly Kitchens, PhD, noted that the Applicant requested a biowaiver request based on the following: a) the proposed drug product is an iso-osmotic sterile solution intended solely for intravenous administration that has the same active ingredient in the same strength as the listed drug and b) the dosage form, route of administration and dosing regimen for the proposed drug are the same as the listed drug.

Based on the evaluation of the submitted information, Dr. Kitchens has granted waiver for in vivo bioavailability/bioequivalence studies and recommends approval of the NDA.

6.0 Clinical Microbiology

As noted by Dr. Kerian Grand Roche, the resubmission provides no new clinical microbiology information. Dr. Roche recommends approval of the NDA and suggests removal of information related to treatment in section 12.4 of the proposed labeling as the current product is indicated only for preoperative prophylaxis.

7.0 Clinical Pharmacology

No new clinical pharmacology data was provided in the NDA. Dr. Kunyi Wu recommends approval of the NDA and notes labeling edits to Section 2.2 (Patients with renal impairment) and Section 7 (Drug interaction).

7.0 Clinical Efficacy/Safety

The resubmission did not provide new clinical or statistical information. Dr. Peter Kim, MD MS, clinical reviewer for this application, recommends Approval of the NDA. Dr. Kim's review provides the D & A section of B. Braun's PI to indicate that the 2 g dose is only approved or (b) (4). Dr. Kim notes that the reported adverse events are consistent with the adverse reactions noted in B. Braun's PI. Additionally, Dr. Kim's review of literature and FAERS search did not provide any additional safety information for this product. (b) (4) However, as noted in Dr. Kim's addendum, given that 2 g cefazolin will only be administered before surgery (b) (4). Therefore, the indication has been revised to preoperative prophylaxis. Also, the label will instruct the use of the drug product in entirety and not any fraction thereof. The Applicant has accepted all recommended labeling revisions.

No statistical review was performed by Christopher Kadoorie, Ph.D., the statistics reviewer since no clinical data was provided in the NDA. Dr. Kadoorie concurs with Dr. Kim's assessment and recommends approval of the NDA.

8.0 Labeling

All labeling issues have been adequately resolved based on reviews from several offices including, the Division of Medication Error Prevention and Analysis (DMEPA) (reviewed by Sevan Kolejian, PharmD). The key recommendations from DMPEA include removing the abbreviation IV to read as "Intravenous" and revising "(b) (4) to "contains 6 units of single-use bags". As indicated above, all labeling recommendations were accepted by the Applicant.

9.0 Pediatrics

This NDA does not meet the criteria required under the Pediatric Research and Equity Act (PREA), and is, therefore, exempt from PREA requirements.

10.0 Other Regulatory Issues

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC) as there were no issues requiring input from the AIDAC.

11.0 Recommended Regulatory Action

This reviewer agrees with the recommendations made by the review team that this NDA covered under 505(b)(2) be approved, relying on the Agency's prior findings of safety and effectiveness of the RLD (NDA 050779).

Balajee Shanmugam -S

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