CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211413Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 131420

**MEETING REQUEST-
WRITTEN RESPONSES**

HQ Specialty Pharma Corporation
Attention: Jeanne Squeglia
Vice President Technical
120 Route 17 North, Suite 130
Paramus, NJ 07652

Dear Ms. Squeglia:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Cefazolin for Injection, USP, 2 g vial.

We also refer to your submission dated June 30, 2016, containing a pre-NDA meeting request. The purpose of the requested meeting was to discuss the submission of a 505(b)(2) new drug application for Cefazolin for Injection, USP.

Further reference is made to our Meeting Granted letter dated July 20, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your July 28, 2016, background package.

If you have any questions, call Kristine Park, PhD, Regulatory Health Project Manager, at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA meeting
Application Number:	PIND 131420
Product Name:	Cefazolin for Injection, USP, powder for solution, 2 g vial
Indication:	Perioperative prophylaxis
Sponsor/Applicant Name:	HQ Specialty Pharma Corporation
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

The proposed indication for Cefazolin for Injection, USP, is for perioperative prophylaxis. The purpose of this pre-NDA meeting is to discuss the submission of a 505(b)(2) new drug application (NDA). The difference between this proposed product and the reference listed drug (RLD) is that this product can be diluted in various diluents based on patient needs. The Sponsor plans to submit the NDA during the 1st quarter of 2017.

2.0 QUESTIONS AND RESPONSES

2.1. Regulatory/Procedural

Question 1.a: HQ will base its NDA for Cefazolin for Injection on the safety and efficacy data of Cefazolin 250 mg, 500 mg, 1 gram, 5 g and 10 g dosage strengths marketed as Ancef by GlaxoSmithKline, NDA 050461, and Cefazolin for Injection USP and Dextrose Injection USP 1g, 2g as marketed by BBraun Medical Inc. NDA 050779 and its subsequent safety and efficacy supplements as well as supporting relevant published literature. The HQ NDA will contain CMC data in support of the drug product formulation. Does the FDA agree with referencing both NDAs in support of the NDA 505(b)(2) filing? Does the FDA concur with the overall content of the HQ Cefazolin for Injection NDA based on Section 505(b)(2) of the FD&C Act?

FDA Response: The 505(b)(2) pathway is a reasonable regulatory approach. A 505(b)(2) application can rely on the findings of safety and effectiveness for more than one listed drug. The safety and effectiveness of any differences between the listed drug and the drug proposed in the 505(b)(2) application must be supported by adequate data, including clinical or nonclinical data, as appropriate.

Question 1.b: HQ intends to submit a new 505(b)(2) application for a formulation of Cefazolin for Injection 2 g that differs from the currently marketed B Braun drug (in both the container

closure and in addition to the possible diluents used). Does the FDA agree that the submission will not require additional clinical studies to support the approval of HQ Cefazolin for Injection 2 g Injection NDA based on Section 505(b)(2) of the FD&C Act?

FDA Response: See the response to question 3b. Provide the requested data so that a determination can be made regarding the appropriateness of a biowaiver. If it is determined that a biowaiver could be granted, additional clinical studies are not likely to be required.

2.2. Preclinical

Question 2.a: Is the proposed nonclinical approach based upon the review of the data from published literature sufficient to support a 505(b)(2) NDA filing for HQ's proposed Cefazolin for Injection 2 g, for the proposed indication?

FDA Response: Yes, it is likely this would be acceptable; however, you should also plan to reference nonclinical information from the RLD package insert, particularly with regard to carcinogenesis/mutagenesis and pregnancy. The adequacy of the proposed literature search strategy will be determined upon review of your NDA.

No additional nonclinical studies will likely be required as long as the impurity and degradation profiles of your new formulation meets or exceeds specifications for the RLD and the detected impurities in your stability studies with the final formulation do not exceed levels in the RLD. Additional nonclinical studies with complete toxicokinetic and histopathologic assessments may be required to explore any unexpected toxicities encountered during development, or to qualify any new impurities, degradants, or novel excipients detected in your final, clinical formulation that are different from the RLD.

You should refer to ICH Guidance Q3B(R2) "Impurities in New Drug Products" for additional information on impurities.[1]

2.3. Clinical (Efficacy and Safety)

Question 3.a: Is the proposed clinical approach based upon the review of the data from published literature, reference to FDA's previous determination of nonclinical safety and efficacy by reference to Ancef by GlaxoSmithKline, NDA 050461, and Cefazolin for Injection USP and Dextrose Injection USP as marketed by B Braun Medical Inc. NDA 050779 sufficient to support a 505(b)(2) NDA filing for HQ's proposed Cefazolin for Injection 2 g for the proposed indication?

FDA Response: Your proposal for the 505(b)(2) application to rely on the findings of efficacy and safety by reference to NDA 050461 and NDA 050779 is reasonable. Further data from published literature are not required for efficacy. However, you need to submit safety updates from published literature.

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[1] ICH Guidance Q3B(R2) Impurities in New Drug Products.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

Question 3.b: HQ intends to request a waiver of evidence of in vivo bioavailability or bioequivalence in accordance with the provisions of 21CFR§320.22. Does the Agency agree with the waiver of bioavailability or bioequivalence?

FDA Response: Your plan to submit a biowaiver request for the proposed drug product under 21CFR§320.22 may not be appropriate due to the difference in qualitative and/or quantitative composition; however, it appears reasonable to submit a biowaiver request under 21CFR§320.24(b)(6). In your NDA, provide the biowaiver request with the following supporting data/information:

- A side-by-side comparison between your proposed drug product and the listed drug products in terms of qualitative and quantitative composition;
- Comparison of the physiochemical characteristics (i.e. pH and osmolality) of the reconstituted and diluted injectable solutions between your proposed drug product and the listed drug products;
- Justification that any differences in formulation or diluent between your drug product and the listed drug products do not affect in-vivo drug disposition.

Note that we will assess the biowaiver request based on the data and justification submitted in the NDA.

2.4. Chemistry, Manufacturing and Controls (CMC)

Question 4.a: It is HQ's intention to submit three registration batches, finished product release testing, and stability data for the NDA filing. Stability data reported at time of filing will consist of (b) (4) (b) (4) (b) (4). The proposed expiration dating at the time of filing will be (b) (4) months. Does the Agency concur that this approach is adequate for filing and review for approvability of the NDA for Cefazolin for Injection 2 g?

FDA Response: No, we do not agree. We recommend that at the time of NDA submission you provide a complete stability data package that includes at least 12 months of long-term and 6-months of accelerated stability data for three (3) representative drug product batches as per ICH Q1A (R2) Guidance. The drug product stability study should include vials stored in both upright and inverted positions. Note that the shelf life for the drug product will be determined based on the assessment of the stability information submitted in the NDA.

We recommend that the three primary stability batches of the drug product be manufactured using three different lots of cefazolin.

Your proposed stability study protocol does not include reconstitution time testing for several time points, e.g., 3, 6 months etc. at 25°C/60% RH. Include test for reconstitution time at all test intervals in the proposed stability protocol.

Question 4.b: The current reference listed drug (RLD) of Cefazolin for Injection USP and Dextrose Injection USP by BBraun is diluted, prior to administration, in 4 % and 3 % dextrose for the 1 g and 2 g dosages, respectively. The comparability study between HQ's proposed Cefazolin 2 g/vial and RLD will be performed as indicated below in order to compare equal dosage with similar concentration of diluent and final solution:

DRUG PRODUCT	RLD
Cefazolin Sodium for Injection (2g/vial) in 5% Dextrose solution – 50 mL	Cefazolin Sodium Solution 2 g in 50 mL single dose in 3% Dextrose

HQ is proposing additional diluents as listed in Table 1 above. The diluents we propose are the same as the diluents listed in the Cefazolin Sodium Vial Package Insert (PI) GlaxoSmithKline, NDA 050461, which was discontinued not for safety or efficacy (new RLD assigned by FDA is Hospira ANDA 065226).

Analyzing the concentration reported in PI, the most concentrate solution is the primary constituted solution (330 mg/mL). This concentration will be considered the worst case. The comparability with the other diluted preparations will be guaranteed by comparison between Cefazolin for Injection data at the concentration of 330 mg/mL vs. the Hospira RLD at the same concentration of 330 mg/mL. This data will be used to demonstrate the stability of Cefazolin after (b) (4) hours at room temperature or for (b) (4) days if stored under refrigeration (5°C or 41°F) as instructed in PI. The compatibility will be conducted using the below listed diluents:

10% Dextrose Injection, USP – 50 mL
5% Dextrose solution – 50 mL

(b) (4)

Tests to be performed on the reconstituted product:
- Assay – in House
- pH USP <791>
- Particulate Matter USP <788>
- Visual
- Related Substances (only for information)

Does the Agency concur that this approach is adequate to include various diluents as listed in above Table 1 in our product insert?

FDA Response: Your proposal to test all the proposed diluents to support the drug product stability when stored under ambient condition (25°C) for (b) (4) hours and when stored in a refrigerator (2 to 8°C) for (b) (4) days is acceptable. However, your proposal to perform these studies (b) (4) is inadequate. Since stability of cefazolin may be concentration dependent, include the highest and lowest concentrations of cefazolin dosing range to support in-use stability of the drug product.

In addition, microbiological studies in support of the post-constitution time (as stated above) will need to be performed. This will require a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions ((b) (4) hours at room temperature and (b) (4) days at 5°C). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A (R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Include a description of the test methods and results of studies that are designed using a minimum countable inoculum ((b) (4) CFU/mL) to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 $\log_{10}$, however other evidence of growth may be significant. Perform the test using the storage conditions (temperature and duration) and diluents specified above. Provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. Provide a positive control that demonstrates the viability of the organisms over the duration of the test period. The RLD may be tested in parallel to demonstrate equivalence.

Additional Comments:

1. Please note that as of June 30, 2015, all labeling for Human prescription drugs and biologic products must comply with requirements of the Pregnancy and Lactation Labeling Rule (PLLR)(Final Rule, Dec. 2014). You will need to submit labeling to be in compliance with current PLLR requirements.

   A link to the Final Rule in the Federal Register is as follows:
   https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

   Also, the following FDA Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug may be helpful to you.
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

2. The production of the drug product and drug substance should ensure the microbiological quality of the drug product through validation of the aseptic manufacturing process. For more details, refer to the following documents:

- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf
- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice (2004) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

3. Provide results of the extractable/leachable studies for the proposed container closure system using screening analytical methods (such as HPLC, GC etc.), and the results of the leachable studies on at least one drug product stability batch through expiry. Perform one time extractable/leachable study using aqueous buffer to cover the pH range of the proposed diluents to be used as reconstitution agents. The duration of this study should be equivalent to the in-use period of the drug product. Place the constituted solutions in inverted position for the leachable study. Refer to USP <1663> and <1664> for the assessment of leachables in the drug product from the container closure system.

4. It is recommended that either one specific identity method or two non-specific tests (follow ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products) be used. For example, two chromatographic procedures, where separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, are generally acceptable.

5. Provide impurity specification as per ICH Q3B (R2) format.

3.0 Additional Application Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements.

Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft 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).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the

message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/

SUMATHI NAMBIAR
08/26/2016