CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211413Orig1s000

OTHER ACTION LETTERS

NDA 211413

COMPLETE RESPONSE

HQ Specialty Pharma Corporation
Attention: Stephanie Boffa
Vice President Regulatory
120 Route 17 North, Suite 130
Paramus, NJ 07652

Dear Ms. Boffa:

Please refer to your new drug application (NDA) dated and received on December 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefazolin for Injection USP, 2 g/vial.

We acknowledge receipt of your amendment dated July 09, 2020, which constituted a complete response to our December 26, 2019, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NONCLINICAL

Unless otherwise justified, nonclinical studies conducted to qualify the safety of leachables should be designed such that the identified leachables are administered in a clinically relevant manner at levels that are equivalent to or greater than what patients would be administered when incorporating interspecies allometric scaling. The information provided in your complete response does not adequately qualify the safety of the identified leachables with your drug product. Specifically:

1. The 14-day toxicity study in rats does not achieve clinically relevant leachables exposures, with animals receiving < (b) (4) of the leachables/day when compared with the maximum estimated daily leachables exposure in patients. While the evaluation of analyzed concentrations in leachable study TE190276 in comparison with the 14-day toxicity study TE192771 based on the GC/MS analysis is informative, it does not address the observed differences in daily exposures to the animals versus maximum estimated daily exposures in humans when accounting for interspecies allometric scaling.
2. You have proposed an acceptable intake of (b) (4) mcg/day for the identified (b) (4) leachables (Toxicological Assessment Annex 5). As previously communicated to you, while it is recognized that PQRI-

PODP has proposed higher qualification threshold levels for leachables, the FDA recommends 5 mcg/day as the qualification threshold for non-genotoxic leachables.

3. You applied [redacted] on the PQRI limit of [redacted] mcg/day to calculate acceptable intake for the [redacted] that would allow for sufficient safety margins. However, this approach is not considered adequate as the application [redacted] has not been considered for regulatory decisions on the qualification of leachables (or impurities) for safety.
4. You applied [redacted] to estimate that the total exposure of the API and related leachables to the rats during the 14-day toxicity study is approximately [redacted] times higher than what a patient would receive following administration of 8 g in a single day and proposed a change in labeling [redacted]. Given the unknown toxicity of the identified leachables, it cannot be assumed that lower daily doses of API and related leachables over the 14-day study in rat would adequately address the safety concerns of the higher leachables exposures associated with an 8 g dose in a single day.
5. The surrogates chosen for use in your read-across analysis with worst-case scenario substances (submitted December 8, 2020), do not contain sufficient toxicology information to qualify the identified leachables for safety. The [redacted] surrogates included in the read-across assessment are not considered acceptable and there are insufficient toxicity data available for [redacted] to predict any potential leachables toxicity. Because the [redacted] cannot be fully characterized, there is considerable uncertainty regarding the structural similarity of the chosen surrogate compounds (i.e., active pharmaceutical ingredient [API] and [redacted] which further limits the utility of the read-across approach.

<u>Information needed to resolve the deficiencies</u>

Given the absence of sufficient toxicity information surrounding the identified leachables, and the feasibility issues precluding adequate structural characterization of the [redacted], you will need to conduct an additional general toxicity study, in an appropriate animal species, for any leachable that exceeds the safety qualification threshold of 5 mcg/day. Such a study should be designed to achieve leachables exposures that are clinically relevant. The potential challenges of the API masking potential toxicity associated with the leachables exposure are acknowledged, but we believe it is feasible to design a nonclinical study that will allow for an adequate safety assessment of the leachables and/or identify any leachables-related shifts in the toxicity profile associated with the API. For example, you may consider conducting a toxicity study of 14-day duration in a larger animal species that would allow for a larger volume of the drug product containing leachables from the [redacted] rubber stopper to be administered. As indicated in the teleconference held on November 30, 2020, we strongly recommend that you submit a draft study protocol for the Agency to review and provide feedback prior to initiating any additional nonclinical studies. Providing a draft protocol for comment will help you to design a study that can best

inform on the safety of the identified leachables when administered at clinically relevant exposures.

Submit a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals are qualitatively and quantitatively similar to the identified leachables described in Study Report TE190276. If any additional leachables are characterized on further testing, or if there are any revised structures and/or identification of any new structures of leachables compared with those identified in your previous leachables assessment (TE 190276), plan to conduct additional (Q)SAR evaluation(s) for bacterial mutagenicity. A follow-up Ames test (bacterial reverse mutation assay) is recommended to qualify leachables that exceed 120 mcg/day with identified structural alerts for genotoxic potential.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
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/

SUMATHI NAMBIAR
01/08/2021 08:44:20 AM

NDA 211413

COMPLETE RESPONSE

HQ Specialty Pharma Corporation
Attention: Stephanie Boffa
Vice President Regulatory
120 Route 17 North
Paramus, NJ 07652

Dear Ms. Boffa:

Please refer to your new drug application (NDA) dated and received on December 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefazolin for Injection USP, 2 g/vial.

We acknowledge receipt of your amendment dated July 02, 2019, which constituted a complete response to our October 19, 2018, action letter.

We also acknowledge receipt of your amendment dated December 6, 2019, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(A) The leachables have not been adequately quantified or characterized. Qualify all leachables above the Analytical Evaluation Threshold (AET) for the proposed cefazolin drug product and provide supporting data to justify the safety of the [redacted] (b) (4) stoppers.

The following are the specific deficiencies and recommendations to address our concerns regarding the leachable study:

1. [redacted] (b) (4) could not be detected by HC-GC-MS analysis when the pharmaceutical matrix was spiked [redacted] (b) (4) (MST study). [redacted] (b) (4) [redacted] (b) (4) It is not clear why

the proposed analytical method can detect (b) (4) in the extractables study, but not in the MST samples. We are concerned about the accuracy of maximum reported levels of (b) (4) for the neat extractable study samples. Evaluate the suitability of the proposed analytical method further and define the LOD and LOQ levels for (b) (4) testing (both for neat samples and for the pharmaceutical matrix). Additionally, as appropriate, evaluate alternate analytical methodologies for detection and quantification of (b) (4) in the leachable study samples.

2. The characterization data for (b) (4) are inadequate. Comments regarding the characterization data in Annex 2 of your submission dated October 15, 2019 are listed below:

   i. You have not provided comparative mass spec (or any other structure specific characterization data) with standards to confirm the structure of these two leachables. Re-evaluate the suitability of your proposed GC/MS method for qualification of these two leachables. Provide appropriate comparative characterization data for the standards and leachable study samples to confirm the structures of (b) (4). Submit the complete analytical method details, i.e., sample preparation, analytical conditions, raw characterization data, etc. for both analytical standards and leachable study samples. Additionally, provide the overlaid spectra of standards and samples with clear and legible peak patterns.

   ii. The total ion chromatograms for leachable study samples and MST samples, in Figure 1, do not show any clear peak between retention time (RT) (b) (4)

   (b) (4)

3. Establish the LOD and LOQ values for the reported leachables with the GC/MS and HS-CG/MS analytical methods to confirm that these methods are suitable to detect all leachables at the reported levels. (b) (4)

   (b) (4)

   Clarify the spiked concentration (and % recovery) of the standards for the MST study. We recommend you spike the MST study samples with higher concentration of the standards and then provide overlay of total ion-

chromatograms for MST samples and leachable study samples. List the studied concentration of MST samples in the total ion- chromatograms.

4. The retention time for the leachable [redacted] in the MST samples does not match the leachable study samples [redacted] Provide adequate supporting characterization data to confirm the structure of [redacted].

5. [redacted] Please provide the complete mass spec data to confirm the identification of [redacted] compound in the leachable study samples.

6. [redacted] Provide details regarding how the recovery correction factors for all the leachables were calculated.

7. We acknowledge that you have provided additional mass spectra using different analytical techniques (GC-MS, GC-EI-QTOF and GC-CI(CH4)-QTOF MS) [redacted]. However, the data only confirm the molecular weight or fragmentation pattern of these [redacted] but not the structures. As recommended previously in the information request dated September 24, 2019, obtain the analytical standard of [redacted] and perform detailed characterization studies of analytical standards and leachable study samples using various analytical technologies (i.e., HPLC, MS and NMR) to confirm the structure of [redacted] as potential leachables. Provide complete analytical method details (e.g., sample preparation, analytical conditions, raw characterization data, etc.) for both analytical standards and

leachable study samples. Also, provide the overlaid spectra of standards and samples with clear and legible peak pattern.

8. You proposed to apply the ICH Q3B limits to justify the safety of cefazolin [redacted] (Annex 2, submission dated October 15, 2019). [redacted] ICH Q3B limits do not apply. Provide appropriate data to justify the safety of these [redacted].

NONCLINICAL

(B) You have not adequately qualified the safety of the identified leachables detected with your drug product.

The following are the specific deficiencies and recommendations to address our concerns regarding the leachable study:

1. Your approach to rely on QSAR analysis to qualify the identified leachables is not adequate. Other than for mutagenicity, QSAR assessments for general toxicity endpoints (i.e., respiratory sensitization, hepatotoxicity, nephrotoxicity, etc.), while informative, are not adequate to support safety of the identified leachables. In the absence of any additional toxicity information for the identified leachables in the published literature or public toxicological databases, a safety qualification threshold of 5 mcg/day for leachables detected in parenteral products is recommended.

2. For the identified leachables containing API fragments [redacted], you applied ICH Q3B qualification threshold of 0.15%. As noted in the product quality comments above, [redacted] the ICH Q3B limits do not qualify the safety of the leachables [redacted].

3. Given the lack of available toxicity information regarding the identified leachables, as indicated in our Complete Response letter dated October 19, 2018, and information request dated July 23, 2019, we recommend that you conduct a general toxicity study for any leachable that exceeds the safety qualification threshold of 5 mcg/day. For example, you may consider conducting a toxicity study of 14-day duration in one species, using isolated leachables or the API enriched with the identified leachables, administered in a clinically relevant manner at leachable levels equivalent to or greater than what patients would be administered.

An Ames test and in vitro mutagenicity and/or mammalian chromosomal aberration assay (i.e., Mouse Lymphoma Assay) are recommended to qualify leachables that exceed 120 mcg/day with identified structural alerts for genotoxic potential. Test the synthesized or isolated leachables to achieve the highest test concentrations recommended for an ICH-compliant bacterial mutagenicity assay according to the current testing guidelines for each genotoxicity assay. For QSAR analysis conducted to predict bacterial mutagenicity of leachables > 120 mcg/day, use the latest versions of the QSAR software and knowledge databases available and submit the complete QSAR reports.

Refer to FDA Guidance for Industry 'S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use' (https://www.fda.gov/media/71980/download) and OECD Genetic Toxicology Guidance Document (https://www.oecd.org/chemicalsafety/testing/Genetic%20Toxicology%20Guidance%20Document%20Aug%2031%202015.pdf) for additional information.

We acknowledge receipt of your Final GLP Report: 19-02803-G1: "14-Day Toxicity Study Via Intravenous Injection in Sprague Dawley Rats with 14-Day Recovery," assessing the difference in the safety profiles of potential leachates from the (b) (4) stopper on December 6, 2019. This amendment was not reviewed as the report was provided late in the review cycle. As stated above, you may reference this submission in any resubmission to this NDA.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the Cefazolin for Injection USP under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Cefazolin for Injection USP Include an updated estimate of use for Cefazolin for Injection USP marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65**.** You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
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/

SUMATHI NAMBIAR
12/26/2019 11:44:58 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211413

COMPLETE RESPONSE

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

Dear Ms. Squeglia:

Please refer to your New Drug Application (NDA) dated December 21, 2017, received December 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefazolin for Injection USP, 2 g/vial.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You have not provided adequate information to support the safety of 2-gram cefazolin [redacted] (b) (4)

NONCLINICAL and PRODUCT QUALITY

Leachables

2. You have not provided adequate support for the assigned structures of the leachables. The original program assigned CAS numbers to both leachables that could not be found in the literature or databases. In your response dated September 14, 2018, you confirmed that the program used in the leachables study erroneously provided the CAS numbers, and that both leachables do not have CAS numbers. Also, no information was provided regarding the validity of the assigned structures of the leachables from this program. Since neither of these leachables are identified in the literature, it is not clear how the structures of these leachables were assigned.

In the absence of valid, reliable structures for the two leachables that exceed the safety qualification threshold of 5 mcg/day, the results obtained using the computational QSAR methodology and read across toxicology assessments with structurally similar compounds and hydrolysis products are of questionable utility.

Information needed to resolve the deficiency

- Additional characterization data should be submitted to support the structures of these leachables. Refer to USP <1663> and USP <1664>.
- Once you have provided additional characterization data to support the proposed structures of these two leachables or have included revised structures with greater structural certainty, conduct additional QSAR evaluation(s) and revised comprehensive toxicological assessment(s) to justify the safety of these identified compounds as needed.

3. The acceptability of the proposed stopper cannot be determined until the identity of the leachables has been established, and the safety profile of the leachables is considered acceptable from a nonclinical perspective.

Impurities

4. The drug product specifications provided in the September 14, 2018 amendment, with the unspecified impurities (RRT (b) (4)) above the identification and qualification thresholds, are inadequate. The referenced ANDA Guidance is not applicable to this NDA.

   Information needed to resolve the deficiency

   - Qualification data should be submitted for all impurities above the qualification threshold.
   - Additional nonclinical studies may be needed to qualify any impurities that exceed the safety qualification threshold described in ICH Guidance Q3B(R2) 'Impurities in New Drug Products'.[1]

5. No characterization data or descriptions of laboratory studies demonstrating efforts to identify the structures were submitted for the specified unidentified impurities in the drug product specifications. The only information provided for these impurities was the relative retention time (RRT). This is not adequate, as the impurities are above the identification threshold.

   Information needed to resolve the deficiency
   Submit the characterization data for the unidentified specified impurities above the identification threshold in the drug product specifications.

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf

6. The analytical procedures were updated to describe the measurement of the three specified unidentified impurities, but the method was not validated for the measurement of these unspecified impurities.

   Information needed to resolve the deficiency
   The analytical methods should be validated for the measurement of the specified impurities in the drug product specifications.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

Container Label

To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:

DDMMMYYYY (e.g., 31JAN2013)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013- JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

Carton Label

Include the lot number statement and expiration date. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. For the format of the expiration date, we recommend using a format like either:

DDMMMYYYY (e.g., 31JAN2013)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013- JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

Carton and Container Labels

1. We recommend that the barcode on the container label be oriented in the vertical position to improve scannability, as barcodes placed in a horizontal position may not scan due to the curvature of the container. Additionally, we request that you add the product barcode to the carton labeling.

2. To provide differentiation between the carton and vials within the carton, revise the NDC package code numbers (last 2 digits) so that the container (vial) label and carton labeling NDC numbers are different. Additionally, if you opt to change the carton labeling NDC, update the NDC number in Section 16, How Supplied/Storage and Handling of the Full Prescribing Information as appropriate.

3. Add the Centigrade symbol (C) following 20° and 2° and Fahrenheit symbol (F) following 68° and 36° within the storage information to provide clarity. For example, "**Before reconstitution store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. After reconstitution**: Stable for (b) (4) hours at room temperature or (b) (4) days if refrigerated 2°C to 8°C (36°F to 46°F)."

4. To minimize the potential for misinterpretation of the equivalency statement, we recommend replacing all instances of the abbreviation "g" with the intended meaning "grams." For example, "…equivalent to 2 grams of cefazolin."

5. Relocate the statement "**PROTECT FROM LIGHT"** such that it follows the "Before reconstitution" storage statement. For example, "**Before reconstitution store at….Room Temperature]. PROTECT FROM LIGHT. After reconstitution: Stable**…"

6. Add the appropriate package type (i.e., Single-Dose Vial) to the principal display panel (PDP).

7. Revise the statement (b) (4) on the PDP to read "Single-Dose Vial – Discard Unused Portion." Additionally, we recommend that you bold the font of the statement "Discard unused portion" to increase the prominence of this important information. For example, "Single-Dose Vial – **Discard Unused Portion**."

ADDITIONAL COMMENTS

In the Pre-NDA meeting minutes dated August 26, 2016, the Division noted that your presentation of cefazolin powder in a 2-gram vial would not trigger the Pediatric Research and Equity Act (PREA). (b) (4) (b) (4) (b) (4) In your complete response, please address your plans for pediatric assessment.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
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4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

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lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jacquelyn Rosenberger, PharmD, Regulatory Project Manager, at (301) 796-9179.

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

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/

SUMATHI NAMBIAR
10/19/2018