

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216109Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary - Addendum

1. Application/Product Information

NDA Number.	216109
Applicant Name	Hikma Pharmaceuticals USA Inc.
Drug Product Name	Cefazolin for injection
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	2 gram/vial and 3 gram/vial
Route of Administration	Intravenous
Maximum Daily Dose	1 gram to 1.5 grams every 6 hours (<i>in rare cases up to 12 grams of cefazolin per day have been used</i>)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of the following infections caused by susceptible isolates of the designated microorganisms in adult and pediatric patients older than 1 month of age for whom appropriate dosing with this formulation can be achieved: • Respiratory tract infections • Urinary tract infections • Skin and skin structure infections • Biliary tract infections • Bone and joint infections • Genital infections • Septicemia • Endocarditis Perioperative prophylaxis in adult patients
Drug Product Description	The proposed drug product, Cefazolin for Injection USP, 2 gram/vial and 3 gram/vial, is a sterile lyophilized powder for injection, intended for intravenous infusion administration after reconstitution and further dilution. The Applicant has not conducted any clinical safety or efficacy studies and instead relies on the safety and efficacy of the listed drug (LD) GlaxoSmithKline's NDA 050461 for Ancef® (cefazolin sodium) for Injection, 1 gram/vial. Except for the strength, the proposed drug product is presented as the same dosage form and contains the same ingredients as the LD, Ancef®.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	CRT: 25°C/60% RH		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Kanny Wan	Katherine Windsor
	<i>Drug Product/ Labeling</i>	Hudson Roth	David Claffey
	<i>Manufacturing</i>	Ephrem Hunde	James Norman
	<i>Biopharmaceutics</i>	Anitha Govada	Elsbeth Chikhale
	<i>Microbiology</i>	Kelly Ann Miller	Erika Pfeiler
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Anh-Thy Ly	
	<i>ATL</i>	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months

b. Additional Comments for Action: N/A





Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided comprehensive CMC information for the proposed drug substance (cefazolin sodium) and the drug product (cefazolin for injection). Also, the overall facility recommendation (OMIR) was entered as “Approve” into Panorama on February 10, 2022. However, the initial OPQ recommendation in the review dated August 29, 2022, was Complete Response due to the pending assessment by the Pharmacology/Toxicology (P/T) team of the qualification information submitted by the Applicant for several leachables identified in the drug product leachable studies (*for details refer to the OPQ Review dated August 29, 2022, in DARRTS*). The qualification information provided for these leachables has been now found acceptable by the P/T review team (*refer to the P/T Review dated September 19, 2022, in DARRTS*). Therefore, the NDA is now recommended for **Approval** from the Product Quality perspective.

Note this OPQ Review Addendum contains Quality Labeling Review and an Addendum to the Drug Product Review only. For all other individual discipline reviews refer to the OPQ Review dated August 29, 2022, in DARRTS.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments: N/A

7 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

NDA 216109

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Required information is missing in several sections of the labeling. The details are provided in the tables below. These recommendations have been conveyed to the project manager; labeling negotiations with the Applicant are ongoing.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	Revise to include dosage form, package type, and amount of active form present. Current: (b) (4) Revised: "For injection: 2 grams or 3 grams of cefazolin as a powder in single-dose vial for reconstitution"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	Package type terminology should be added – refer to recommendation above.

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Remove the statement (b) (4) (b) (4)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Inadequate	Revise the refrigeration temperature Current: (b) (4) Revised: "...if stored under refrigeration at 2°C to 8°C (36°F to 46°F)." Include "Discard unused portion" as product is packaged in single-dose vials. Revise approximate reconstituted concentrations to reflect new drug product fill weights: For the 2 g/vial, change (b) (4) to 136 mg/mL For the 2 g/vial, change (b) (4) to 196 mg/mL The volumes in Tables 1-4 need to be adjusted based on these new concentrations
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and</i>	Inadequate	1.) Must include the regulatory statement as worded in 21 CFR 201.57(c)(3). Current: (b) (4)

<i>discoloration prior to administration, whenever solution and container permit</i>		(b) (4) Revised: “Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit” 2.) Move the statement on the identifying characteristics of the reconstituted solution (i.e., color and clarity) from the end of this section to immediately after regulatory statement. Remove (b) (4) statement from description of reconstituted solution (b) (4) Current: (b) (4) (b) (4) Revised: “Reconstituted solutions may range in color from pale yellow to yellow.”
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	Adequate	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement “<i>DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x</i>” with x numerical citation to “OSHA Hazardous Drugs”.	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Remove the statement (b) (4) (b) (4)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Inadequate	Revise to order the description as (1) dosage form, (2) strength(s), (3) identifying characteristics, and (4) limited packaging information. Current: (b) (4) Revised: "Cefazolin for Injection is available as 2 grams or 3 grams of cefazolin as a white to off-white crystalline powder in single-dose vial for reconstitution."
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Inadequate	Package type should be indicated – see above recommendation.

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Inadequate	Include statement: "Cefazolin for Injection is intended for intravenous infusion."
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Inadequate	Salt equivalency statement should be included in this section: "The 2 g/vial Cefazolin for injection contains 2 grams of cefazolin (equivalent to 2.097 g of cefazolin sodium). The 3 g/vial Cefazolin for injection contains 3 grams of cefazolin (equivalent to 3.144 g of cefazolin sodium)." In addition, include the sodium content statements: "The 2 g/vial Cefazolin for Injection contains 96 mg of sodium. The 3 g/vial Cefazolin for Injection contains 144 mg of sodium."
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Sterility statement (if applicable)	Inadequate	Sterility of the product is not stated, include the statement “Cefazolin for Injection is supplied as a sterile powder in single-dose vials”
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Inadequate	The pH of the product is not stated, include the statement “After reconstitution with sterile water for injection, the drug product solution has a pH of 4.0-6.0”

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	Inadequate	Sterility statement required by USP monograph. Refer to recommendation above.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Inadequate	The strength of solids for injection should be expressed in grams/vial.
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Inadequate	Include a description of the drug product appearance and the package type. Current: (b) (4) (b) (4) Revised: "Cefazolin for Injection is available as 2 grams or 3 grams of cefazolin as a white to off-white crystalline powder in single-dose vial for reconstitution." Remove (b) (4) statement (b) (4) (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	Package type should be designated. See above recommendation.
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.” with x numerical citation to “OSHA Hazardous Drugs.”	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Recommend including statement “Storage conditions for reconstituted and diluted solutions of Cefazolin for Injection are described in another section of labeling [see <i>Dosage and Administration</i> (b) (4)].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “ <i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i> ”	N/A	

Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients. Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

² Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Container labels as submitted in SD 15 (eCTD 0015), dated August 23, 2022.

(b) (4)



3.2 Carton Labeling

Carton labels as submitted in SD 15 (eCTD 0015), dated August 23, 2022.

(b) (4)



Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	
Net contents (e.g., tablet count, volume of liquid)	N/A	
“Rx only” displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	The lot, expiration date, and serialization information will be printed at the time of packaging above the carton label directly on the carton.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

The following comments were sent to the Applicant on 08/04/2022 and adequate addressed on 08/15/2022:

- Salt statements are currently: (b) (4)
 Does not adhere to Salt Guidance. Revise to: "Each vial contains the equivalent of 2 g of cefazolin present as 2.097 g of cefazolin sodium. The sodium content is 96 mg." "Each vial contains the equivalent of 3 g of cefazolin present as 3.144 g of cefazolin sodium. The sodium content is 144 mg."

The following comments were sent to the Applicant on 08/18/22 and adequately addressed on 08/23/2022:

- Both carton and contain labels include the following statemen (b) (4)
 (b) (4)
 (b) (4) Revise the text (b) (4)

³ Established name = [Drug] [Route of Administration] [Dosage Form]

(b) (4) To
"Reconstituted solutions may range in color from pale yellow to yellow."

- The container labels include statements on the concentration of the reconstituted drug product solutions. For 2 grams/vial, (b) (4) for 3 grams/vial, (b) (4). A study to determine the concentrations of the reconstituted drug product solutions was provided in the submission dated May 31, 2022. The results of this study indicate an average concentration of (b) (4) mg/mL and (b) (4) mg/mL for the 2 grams/vial and 3 grams/vial dosage strengths, respectively. For 2 grams/vial, revise the test (b) (4) to "The resultant solution will contain cefazolin (b) (4) mg/mL". For 3 grams/vial, revise the test (b) (4) to "The resultant solution will contain cefazolin (b) (4) mg/mL".
- In response, the Applicant proposed to use the updated concentrations of the reconstituted drug product solutions based on the change in the (b) (4) fill weights provided in the submission dated 07/28/2022. The 2 g/vial statement will read "The resultant solution will contain cefazolin 136 mg/mL" and the 3 g/vial statement will read "the resultant solution will contain cefazolin 196 mg/mL". This proposal is adequate.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Highlights of Prescribing Information

- Revise dosage forms and strengths statement and include package type
- Remove (b) (4)

Section 2

- Include statement required as per 21 CFR 201.57(c)(3)
- Put reconstituted solution appearance description after 21 CFR 201.57(c)(3) statement and remove (b) (4) statement
- Revise reconstituted concentrations to reflect data in SD 11 and adjust volumes in Tables 1-4 as needed
- Include refrigeration temperature range
- Include discard unused portion statement

Section 3

- Revise drug product appearance description and include package type
- Remove (b) (4)

Section 11

- Include salt equivalency statement and statements on sterility, pH, and route of administration (intravenous)

Section 16

- Include description of drug product appearance and package type
- Change strength in table from grams to grams/vial
- Remove (b) (4) statement (b) (4)
- Include reference to Section (b) (4) for reconstituted/diluted drug product storage conditions

Detailed on these recommendations are included in the tables above. The comments have been conveyed to the project manager and labeling negotiations are ongoing.

Overall Assessment and Recommendation:

Recommended and required changes to the Prescribing Information from the drug product quality perspective are included in this review and have been conveyed to the project manager for labeling negotiations.

Primary Labeling Assessor Name and Date:

Hudson Roth, Ph.D., 08/11/22

Secondary Assessor Name and Date (and Secondary Summary, as needed):

David Claffey, Ph.D., 08/11/22



Hudson
Roth

Digitally signed by Hudson Roth
Date: 9/23/2022 09:29:52AM
GUID: 6179adc200758f92383849fa56daa5d6



David
Claffey

Digitally signed by David Claffey
Date: 9/23/2022 09:31:15AM
GUID: 508da71e00029e20b201195abff380c2

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/

DOROTA M MATECKA
09/26/2022 09:42:59 PM



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	216109
Applicant Name	Hikma Pharmaceuticals USA Inc.
Drug Product Name	Cefazolin for injection
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	2 gram/vial and 3 gram/vial
Route of Administration	Intravenous
Maximum Daily Dose	1 gram to 1.5 grams every 6 hours (<i>in rare cases up to 12 grams of cefazolin per day have been used</i>)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of the following infections caused by susceptible isolates of the designated microorganisms in adult and pediatric patients older than 1 month of age for whom appropriate dosing with this formulation can be achieved: • Respiratory tract infections • Urinary tract infections • Skin and skin structure infections • Biliary tract infections • Bone and joint infections • Genital infections • Septicemia • Endocarditis Perioperative prophylaxis in adult patients
Drug Product Description	The proposed drug product, Cefazolin for Injection USP, 2 gram/vial and 3 gram/vial, is a sterile lyophilized powder for injection, intended for intravenous infusion administration after reconstitution and further dilution. The Applicant has not conducted any clinical safety or efficacy studies and instead relies on the safety and efficacy of the listed drug (LD) GlaxoSmithKline's NDA 050461 for Ancef® (cefazolin sodium) for Injection, 1 gram/vial. Except for the strength, the proposed drug product is presented as the same dosage form and contains the same ingredients as the LD, Ancef®.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	CRT: 25°C/60% RH		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Kanny Wan	Katherine Windsor
	<i>Drug Product/ Labeling</i>	Hudson Roth	David Claffey
	<i>Manufacturing</i>	Ephrem Hunde	James Norman
	<i>Biopharmaceutics</i>	Anitha Govada	Elsbeth Chikhale
	<i>Microbiology</i>	Kelly Ann Miller	Erika Pfeiler
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Anh-Thy Ly	
	<i>ATL</i>	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

3. Deficiencies - The results of the extractable/leachable studies for the proposed drug product commercial container closure system revealed several leachables, which were detected above the SCT level of 5 µg/day. The recently submitted by the Applicant qualification information for these leachables has not been yet found acceptable by the Pharmacology/Toxicology (P/T) team and, subsequently, the proposed container closure system for the drug product could not be determined as suitable. Therefore, the CMC information provided for the drug product has been found inadequate at this time.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided comprehensive CMC information for the proposed drug substance (cefazolin sodium) and the drug product (cefazolin for injection). The overall facility recommendation (OMIR) was entered as “Approve” into Panorama on February 10, 2022, and no specific Product Quality related deficiencies were identified (with the labeling review still pending). However, the qualification information submitted as part of the extractable/leachable assessment for the drug product container closure system, was consulted with the Pharmacology/Toxicology team and has not been yet found acceptable. Therefore, the NDA is recommended for Complete Response from the Product Quality perspective at this time. *This recommendation may change within this review cycle if/when the leachables qualification information is deemed adequate by the P/T review team.*

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Inadequate
Quality Labeling	-	Pending
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Environmental Assessment: Choose an item.

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: N/A

95 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS REVIEW	
Application No.	NDA 216109-ORIG-1
Type of Submission	505(b)(2)
Applicant/Sponsor	Hikma Pharmaceuticals USA
Product Name	Cefazolin for Injection, USP, 2 g/vial and 3 g/vial
Dosage Form/Strength	Powder for Injection/ 2g/vial and 3g/vial
Route of Administration	Injectable /Intravenous (IV) infusion
Intended Use¹	ANCEF is indicated in the treatment of the following serious infections due to susceptible organisms: Respiratory Tract Infections Urinary Tract Infections Skin and Skin Structure Infections Bone and Joint Infection Genital Infections Septicemia Perioperative Prophylaxis
Submission Date	12/07/2021 (Original Submission)
Recommendation	Adequate

EXECUTIVE SUMMARY:

The proposed drug product, Cefazolin for Injection USP, 2 gram (base)/vial and 3 gram (base)/vial, is a sterilized powder for injection, intended for intravenous (IV) infusion administration after reconstitution and dilution. The Applicant has not conducted any clinical safety or efficacy studies and instead relies on the safety and efficacy of the listed drug (LD) GlaxoSmithKline’s NDA 050461 for Ancef[®] (cefazolin sodium) for Injection, 1 gram (base)/vial. The proposed product contains the same active ingredient (cefazolin) and is presented in the same dosage form, for the same route of administration [IV use only], and indication as the listed drug (LD), GlaxoSmithKline’s NDA 050461 for Ancef[®] (cefazolin sodium) for Injection, 1 gram (base)/vial. The Applicant has not conducted a BA/BE study between the proposed drug product and the LD, and instead relies on composition and physicochemical comparisons between the proposed drug product and the LD.

¹ LD label for NDA 050461-SUPPL-139 (approval date 06/02/2004)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50461slr139_ancef_lbl.pdf

Because the LD is currently discontinued for reasons other than safety or efficacy, the Reference Standard (RS) as identified in FDA's electronic Orange Book (Hikma Farmacêutica's ANDA 065047, Cefazolin for Injection, 1 gram (base)/vial) is used for comparative studies to establish a bridge between the proposed drug product and the RS. The Agency agreed to the use of RS for the physicochemical comparison of drug product in a Type B meeting dated September 9, 2021. The physicochemical comparison of the proposed product with RS to establish a bridge between the proposed product and LD is appropriate because the RS is considered to be bioequivalent to the LD and the LD is commercially unavailable to conduct the tests.

Both the proposed drug product and the LD and RS contain only active drug and no excipients in the vial. The pH and osmolality of the proposed drug product and the RS, after reconstitution (with Water for Injection) and dilution (with 5% dextrose or 0.9% Sodium Chloride Injection), are similar. Therefore, the disposition kinetics of cefazolin are expected to be similar for these two products. The data submitted in the Application demonstrates that the proposed drug product has been adequately bridged to the RS which was approved based on the LD; therefore an in vivo pharmacokinetic study is not needed.

A scientific bridge between the proposed product (Cefazolin for Injection USP, 2 gram (base)/vial and 3 gram (base)/vial) and RS has been established in accordance with 21 CFR §320.24(b)(6).

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 216109 for Cefazolin for Injection USP, 2 gram (base)/vial and 3 gram (base)/vial is recommended for **APPROVAL**.

SUBMISSION:

Hikma submitted the current NDA for Cefazolin for Injection USP, 2 gram (base)/vial and 3 gram (base)/vial under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) Application relies for approval, on FDA's findings of safety and effectiveness for the listed drug (LD), Ancef[®] (cefazolin sodium) Injection, 1 gram (base)/vial. approved under NDA 050461 on 10/4/1973² and has been discontinued.

² <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

BIOPHARMACEUTICS REVIEW:

The LD, Ancyf[®] (cefazolin sodium) Injection, 1 gram (base)/vial, approved under NDA 050461, is a powder packaged in sterile single-use vials containing 1g base of cefazolin, without other excipients. Ancyf[®] is also approved in other strengths, i.e., 250 mg and 500 mg per vial, and pharmacy bulk packaging of 5 gram and 10 gram per vial, however, the approved label only describes the use of the 1 gram and 10 gram per vial strengths.

Ancyf[®] is indicated in the treatment of serious infections (Respiratory Tract Infections, Urinary Tract Infections, Skin and Skin Structure Infections, Biliary Tract Infections, Bone and Joint Infections, Genital Infections, Septicemia, Endocarditis, and Perioperative Prophylaxis) due to different susceptible organisms as indicated in the [LD label](#) available at drugs@fda.gov.

The Applicant (Hikma Pharmaceuticals) developed Cefazolin for Injection, USP, 2 g/vial and 3 g/vial, for use as intravenous infusion **only** as part of a convenience package. It should be noted that the Reference Standard listed in the Electronic Orange Book, Cefazolin for Injection, USP, 500 mg/vial and 1 g/vial approved under ANDA 065047, is owned and manufactured by the same Applicant, Hikma Pharmaceuticals. It is also noted that the LD, Ancyf[®] (cefazolin for injection) and the RS can both be administered intramuscularly or intravenously (bolus or infusion). The Applicant stated that the proposed NDA 216109 is seeking administration as intravenous infusion only. The proposed strengths in the NDA (2 g/vial and 3 g/vial) are submitted for convenience package to allow the use of less vials for patients who need a high dose. This is also an extension of the strengths for the Applicant's currently approved product for Cefazoline under ANDA 065047 for Cefazoline for Injection 500 mg/vial and 1 gram/vial.

The main difference between the proposed drug product and the LD is in the presentation. The LD was marketed as a 1 g/vial, whereas the proposed Hikma's Cefazolin for Injection is in two presentations [different amount/vial] to be supplied as 2 g/vial and 3 g/vial. Both the LD and proposed product have similar directions for reconstitution and dilution prior to intravenous administration and have the same indications. The directions for reconstitution and dilution as described in the label provides for a final concentration of 20 mg/mL that is same as LD and additional concentrations of 30 mg/mL and 40 mg/mL, that are not the same as the LD.

BIOWAIVER REQUEST/BRIDGING:

The Applicant requested a waiver of in vivo bioavailability/ bioequivalence study claiming that there are no differences in the active ingredient, route of administration, dosage form and dosing regimens for the proposed drug product compared to the LD except for the drug product strengths.

The Applicant submitted a biowaiver request (quoting 21 CFR 320.24(b)(6)) along with the supporting information for establishing a bridge between the proposed and RS products.

As suggested in the [IND #155840](#)³ meeting and described in the meeting minutes, dated October 06, 2021, the Applicant was informed that a biowaiver request (under 21 CFR 320.22(d)) does not apply to the proposed drug product, and that the Applicant can try to establish a bridge between the proposed drug product and the LD under 21 CFR 320.24(b)(6). The Applicant submitted justification and supporting data to establish a bridge between the proposed product and the LD products in accordance with 21 CFR 320.24(b)(6).

The proposed drug product is a sterile powder for solution, intended solely for intravenous (by infusion only) administration after reconstitution and dilution, therefore its absolute bioavailability is expected to be 100 percent. The Applicant further claimed that no excipients/inactive ingredients are included in the proposed drug product nor LD; therefore, there is no concern about potential disposition kinetics changes due to excipients.

The Applicant provided comparison of composition and physicochemical parameters between the proposed drug product and the LD/RS as discussed below:

1. Formulation composition comparison (Table 1 and 2)
2. Physicochemical comparison between the reconstituted and diluted solutions of the proposed drug product (concentration 20 mg/mL, 30 mg/mL and 40 mg/mL) and the reconstituted and diluted solutions of the Reference Standard (10 mg/mL and 20 mg/mL) (Table 3 and 4)

The active ingredient, route of administration, dosage form of the proposed drug product are similar to the LD product. Table 1 provides a side-by-side comparison to demonstrate that proposed and LD product are similar.

Table 1: Comparison of composition of the proposed product, Cefazolin for Injection, USP, 2 g/vial and 3 g/vial formulation (NDA 216109) and the LD, Ancef® (cefazolin) for Injection, 1 g/vial (NDA 050461) before reconstitution

Table 1. Formulation Comparison of RLD (Ancef [®]) and RS (Hikma) for Cefazolin for Injection, USP			
Component	Amount per vial		
	RLD (Ancef) (NDA 050461)	RS (Hikma approved ANDA 065047)	Proposed Hikma Product
Cefazolin Sodium	500MG BASE/VIAL	500MG BASE/VIAL	
	1GM BASE/VIAL	1GM BASE/VIAL	
			2 GM BASE/VIAL
			3 GM BASE/VIAL

1g cefazolin base = 1.048 g Cefazolin Sodium

³ <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8061b813&showAsPdf=true>

Table 2: Final concentrations of the LD/RS and the proposed product, Cefazolin for Injection, USP, 2 g/vial and 3 g/vial formulation (NDA 216109) after reconstitution and dilution:

Vial Contents	Amount of Sterile Water for Injection for Reconstitution	Approximate Reconstituted Concentrations	Recommended Diluent Volume	Approximate Final Concentrations
1 gram (LD and RS)	2.5 mL	330 mg/mL	50 mL or 100 mL	10 mg/mL ⁴ or 20 mg/mL
2 gram (proposed)	15 mL	(b) (4)	50 mL or 100 mL	40 mg/mL or 20 mg/mL
3 gram (proposed)	15 mL	(b) (4)	100 mL	30 mg/mL

Table 3 and Table 4 below contain the physicochemical comparisons between the proposed new drug product, 2 g/vial and 3 g/vial of Cefazolin for Injection, USP following reconstitution (with Sterile Water for Injection) and dilution of the reconstituted solution (with either 50 ml or 100 ml of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP), and the previously approved Cefazolin for Injection, USP, 1 g/vial (ANDA 065047) as reference standard (RS), following reconstitution and dilution.

Table 3: Physicochemical comparison of the Hikma’s proposed new drug product (NDA 216109 for Cefazolin for Injection, USP, 2 g/vial and 3 g/vial) and RS (ANDA 065047 for Cefazolin for Injection, USP, 1 g/vial), following reconstitution and dilution in 50 mL or 100 mL (for 2g/vial) and 100 mL (for 3 g/vial) of 0.9% Sodium Chloride Injection.

Cefazolin Presentation	Nominal Concentration (mg/mL)	pH	Average Osmolality (mOsmol/kg)	Density (g/mL)
Cefazolin RS 1g/Vial	10	4.70	296	1.007
	20	4.86	309	1.011
2g /Vial	20	4.66	311	1.011
	40	4.72	338	1.020
3g /Vial	30	4.69	349	1.016

⁴ For the RS product intermittent or continuous infusion, 2.5 mL of sterile water for injection is added to get 3 mL of reconstituted solution with a concentration of approximately 330 mg/mL (b) (4). Entire contents of the vial are diluted in 50 mL or 100 mL infusion solutions to get an approximate concentration of 10 mg/mL or 20 mg/mL (b) (4). (b) (4). (b) (4).

Table 4: Physicochemical comparison of the Hikma’s proposed new drug (NDA 216109 for Cefazolin for Injection, USP, 2 g/vial and 3 g/vial) and RS (ANDA 065047 for Cefazolin for Injection, USP, 1 g/vial), following reconstitution and dilution in 50 mL or 100 mL (for 2g/vial) and 100 mL (for 3 g/vial) of 5% Dextrose Injection.

Cefazolin Presentation	Nominal Concentration (mg/mL)	pH	Average Osmolality (mOsmol/kg)	Average Density (g/mL)
Cefazolin RS 1g/Vial	10	4.73	281	1.017
	20	4.89	298	1.020
2g /Vial	20	4.81	300	1.020
	40	4.77	329	1.027
3g /Vial	30	4.85	341	1.026

Reviewer’s Assessment: Adequate

This 505(b)(2) Application relies, for its approval, on FDA’s findings of safety and effectiveness for the listed drug (NDA 050461 for Ancef®). This NDA 216109 includes information to support the bridge between the proposed drug product and the LD product in accordance with 21 CFR 320.24(b)(6). The Applicant is not seeking any new indications or dosing regimens for the two new proposed strengths (2 g per vial and 3 g per vial) and indicated that both 2g/vial and 3 g/vial will be administered in accordance with the dosing recommendations outlined in the prescribing information (PI) of the LD. No clinical or nonclinical studies were conducted for the proposed drug product; however, summaries of clinical and nonclinical data are submitted in module 2.

The proposed drug product is a parenteral dosage form, powder for solution for administration as intravenous infusion only (Note: LD is also administrated as intramuscular and intravenous bolus). The proposed drug product has the same active ingredient (cefazolin sodium) and no inactive ingredients, has the same dosage form, route of administration and indication as the LD. The directions for reconstitution and dilution differ based on the differences in strength. The volume to be administered by infusion is adjusted for the 30 mg/mL and 40 mg/mL concentrations to achieve the desired dosing. To demonstrate similarity between the proposed product and the listed drug, the Applicant submitted the following supportive data:

1. The proposed cefazolin for injection product is supplied as 2 mg/vial and 3g/vial as compared to the listed drug, Ancef, that is supplied as 1 g cefazolin/vial.
2. The only difference is in the amount of drug substance per vial in the drug product, there are no other excipients/inactive ingredients in the proposed drug product, nor the LD.
3. The reported Osmolality (b) (4), pH ranges (b) (4) of the proposed product after reconstitution and dilution in 0.9% Sodium Chloride Injection USP, or dilution in 5% Dextrose injection, USP, are comparable to the RS Cefazoline 1 g/Vial Osmolality ((b) (4)) and pH ranges ((b) (4)).

Because the formulation of Hikma's Cefazoline 2 g/Vial and 3 g/Vial is identical to the RS (Hikma's Cefazoline 1 g/Vial), and pH and Osmolality are comparable [after reconstitution and dilution], these products are expected to have similar cefazolin disposition kinetics.



Anitha
Palamakula
Govada

Digitally signed by Anitha Palamakula Govada
Date: 7/19/2022 09:47:39AM
GUID: 508da6fc000283db244b623ce9f67aca



Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale
Date: 7/19/2022 02:34:33PM
GUID: 50743ccc000031928b54eba1769a5df9

CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	216109
Assessment Cycle Number	01
Drug Product Name/ Strength	Ancef (Cefazolin)/2 g/vial and 3 g/vial
Route of Administration	IV/IM Injection
Applicant Name	Hikma Pharmaceuticals USA Inc.
Therapeutic Classification/ OND Division	CDER/OD/OID/DAI
Manufacturing Site	Hikma Farmacêutica (Portugal), S.A. Estrada do Rio da Mó 8, 8A, 8B, 2705-906 Terrugem SNT, Portugal
Method of Sterilization	Sterile drug substance, (b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The drug substance is received sterile. Adequate information was provided to support the sterility assurance of the drug product for the intended shelf-life. This includes drug product (b) (4) process (b) (4) qualification, environmental monitoring, container closure integrity testing validation, validation of the sterilization and depyrogenation processes used for containers, closures, equipment, and components, holding periods, release and stability testing method validation and specifications. The DMFs ((b) (4) (b) (4) referenced for sterilization of the drug substance were deemed adequate.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 SD 1	12/7/2021
0002 SD 2	1/24/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a sterile lyophilized powder for injection. The drug substance is received sterile. The drug product is comprised of the drug substance (b) (4)

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- D (b) (4) M08R01, dated 7/24/2018 for review of the sterile drug substance
 - D (b) (4) M03R01.docx, (b) (4)
(b) (4)
 - D (b) (4) M04R01.docx, (b) (4)
(b) (4)
- D (b) (4) M16R01.docx (b) (4)
(b) (4)
- D (b) (4) M17R01.docx (b) (4)
(b) (4)
- D (b) (4) M18R01.docx (b) (4)
(b) (4)
- 065074s15.pdf, dated 6/9/2014 (b) (4)
(b) (4)
- 065238s2.doc, dated 1/25/2013 for review of the (b) (4)
validation studies (b) (4)
(b) (4)
- N209463s007mr01.docx, dated 04/09/2019 for review of SOP QA040
(actions taken following a (b) (4) failure).

S DRUG SUBSTANCE

The applicant provided an LOA from (b) (4) for the manufacturing process for the sterile drug substance (DMF # (b) (4) dated 5/5/2021.

Assessment: Adequate

The manufacturing process of the sterile drug substance was found to be adequate in review D (b) (4) M08R01, dated 7/24/2018. DMF (b) (4) referenced two DMFs for manufacturing of the sterile drug substance ((b) (4) and (b) (4) for manufacturing at plants 1 and 2 respectively). (b) (4) and requalification data for sterilization/depyrogenation processes were deemed adequate in reviews D (b) (4) M03R01.docx, dated 4/20/2021 and D (b) (4) M04R01.docx, dated 12/4/2019 for manufacturing plants 1 and 2.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product** – Section 3.2.P.1- sterile white to off-white powder for injection

- **Drug product composition** – Section 3.2.P.1 for both presentations

Ingredient	Quantity (% w/w)	Function
Cefazolin Sodium, USP	100	Active ingredient

- **Description of container closure system** – Section 3.2.P.1

Configuration	Component	Description	Manufacturer
2.0 g/vial	Vial		(b) (4)
	Stopper		
	Seal		
3.0 g/vial	Vial		
	Stopper		
	Seal		

Note: The CCS for both presentations is identical except for the color of the seal.

Assessment: Adequate

The applicant provided an adequate description of the drug product composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT



14 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDICES: N/A

R REGIONAL INFORMATION

Executed Batch Records

Section 3.2.R

Executed lot #(s):

- 2 g/vial: 120061, 120062, 120063
- 3 g/vial: 120064, 120065, 120066

The batch records confirm that validated (b) (4) process and component sterilization/depyrogenation processes were used for the manufacture of the exhibit batch.

Assessment: Adequate

The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols

No CP was included in the application.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Post-dilution/constitution hold time

Section 1.14.1.3, *proposed-insert pdf*

Storage temperature: 20-25°C (prior to reconstitution)

Maximum storage time: 24 months (unopened)

Route of administration: IM / IV

Container: Single dose

Reconstituted/Further Diluted Drug Product

Reconstitute in sterile WFI, USP

Further product dilution: Sodium Chloride Injection, USP or 5% dextrose injection, USP

Presentation	Reconstitution Concentration (mg/mL)	Final Concentration after Dilution (mg/mL)
2 g/vial	(b) (4)	40
3 g/vial	(b) (4)	30

Maximum Storage time following reconstitution and dilution for both presentations:

- Room temperature: 24 hours
- Refrigerated: 7 days

Section 3.2.P.2, In-use micro study pdf

Microorganisms used and inoculum:

- *S. aureus*: (b) (4) CFU
- *P. aeruginosa*: (b) (4) CFU
- *E. coli*: (b) (4) CFU
- *C. albicans*: (b) (4) CFU
- *A. brasiliensis*: (b) (4) CFU

For the microbial in use study, the most diluted solutions were used (considered worst-case). Vials containing 2 g of the drug product were reconstituted with 15 mL sterile WFI (133.3 mg/mL) and diluted with 0.9% sodium chloride USP or 5% dextrose injection to a final concentration of 20 mg/mL prior to inoculation with microorganisms. Samples were taken at time 0, and after 24 hours at room temperature or 7 days refrigerated.

Acceptance Criteria: No increase in the CFU when compared to time 0 ((b) (4) higher than the initial value measured)

Results:

Diluent	Results	
	24 hr RT	10 days fridge
WFI	No growth in all organisms tested	No growth in all organisms tested
Sodium chloride	No growth in all organisms tested	No growth in all organisms tested
5% Dextrose	No growth in all organisms tested	No growth in all organisms tested

Positive and negative controls were provided and acceptable. Positive control CFUs ranged from (b) (4). Initial counts and final counts were provided and demonstrated < (b) (4) increase for all microorganisms tested.

Assessment: Adequate

The applicant has provided sufficient microbial data to support the reconstitution and dilution storage conditions provided in the product labeling.

Post-Approval Commitments: N/A

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: KellyAnn Miller, PhD, 3/14/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed): Erika Pfeiler, PhD, 3/14/2022



KellyAnn
Miller

Digitally signed by KellyAnn Miller
Date: 3/14/2022 09:41:35AM
GUID: 5e1f6620004382592e50464168938fab



Erika
Pfeiler

Digitally signed by Erika Pfeiler
Date: 3/14/2022 10:09:26AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

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/

DOROTA M MATECKA
08/29/2022 04:46:02 PM