CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208193 (resubmission # 2)
Review # 3

Drug Name/Dosage Form	Ozobax (Baclofen) Oral Solution
Strength	1 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Metacel Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	N/A	
Drug Product/Labeling	Dan Berger	Wendy Wilson-Lee
Manufacturing	Peter Krommenhoek	Nallaperumal Chidambaram
Microbiology	Gouri Chattopadhyay	Elizabeth Bearr
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

Amendments Reviewed

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-020, Resubmission after CR	3/18/2019	All
SD-021, Response to IR	4/1/2019	All
SD-022, Labeling/Container Carton	4/16/2019	Drug Product/Labeling
SD-023, Response to IR	5/29/2019	Microbiology
SD-024, Response to IR	6/14/2019	Drug Product
SD-025, Labeling/Container Carton	7/9/2019	Drug Product/Labeling

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	2/5/2019	Reviewed by Roger Farr
	III			N/A	N/A	Sufficient information in NDA
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	IV			N/A	N/A	Sufficient information in NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	17851	Innovator application for Lioresal (baclofen) tablets referenced under 505(b)(2) for safety and efficacy. Novartis discontinued marketing of Lioresal tablets, and subsequently withdrew the NDA, for reasons not related to safety or efficacy.
IND	112300	Baclofen oral solution, bioequivalence study versus generic baclofen tablets manufactured by Ivax (ANDA 72235). The Office of Generic Drugs (OGD) currently designates the Ivax product as the reference standard for generic baclofen tablets.

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue an Approval letter for NDA 208193, Ozobax® (baclofen) oral solution. From a quality perspective, the product is judged adequate for use provided it is stored refrigerated (2°C to 8°C). The assigned expiration dating period (expiry) for Ozobax is 12 months when stored refrigerated.

II. Summary of Quality Assessments

A. Product Overview

Baclofen was originally developed by Ciba-Geigy (now part of Novartis) for treatment of spasticity resulting from multiple sclerosis. Lioresal® (baclofen) tablets were approved for that indication in 1977 and may also be used for treatment of spasticity resulting from spinal cord injury. Currently, oral baclofen is available as generic 10 mg and 20 mg tablets from multiple suppliers.

The applicant proposes marketing of an aqueous oral solution containing baclofen 1 mg/mL for the same indications as approved for baclofen tablets. The oral solution also contains glycerin, citric acid, sucralose, sodium citrate, methylparaben, propylparaben, and grape flavor as inactive ingredients. Approval of the oral solution would (b) (4)

The oral solution would also be an age appropriate dosage form for study of baclofen in pediatric patients.

Proposed Indication(s) including Intended Patient Population	Treatment of spasticity resulting from multiple sclerosis or spinal cord injury in patient age 12 years and older
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg given as 20 mg four times daily
Alternative Methods of Administration	None

B. Quality Assessment Overview

Background

This is the second resubmission of NDA 208193, which was originally submitted on 1/11/2016 and accepted for review on 3/11, 2016. During the initial review cycle, numerous deficiencies relating to the manufacturing process for the product, the product

specification (including analytical procedures, method validation, and proposed acceptance criteria), conduct and analysis of stability studies, and discrepancies in stability data (b) (4) (b) (4) were identified. A complete response letter (CRL) was issued on 1/11/2017.

The applicant resubmitted the NDA on 1/2/2018. A second CRL, which cited two product quality deficiencies, was issued on 6/25/2018. Specifically, in response to first cycle CRL deficiencies related to (b) (4) (b) (4)

Drug Substance

The bulk drug substance, Baclofen USP, is manufactured by (b) (4) (b) (4) The applicant cross-references (b) (4) DMF (b) (4) for information regarding manufacture and control of the bulk drug substance. Supporting information for the bulk drug substance was deemed adequate during the first cycle review and remains adequate.

Drug Product

The proposed product, Baclofen oral solution 1 mg/mL is an aqueous solution that contains (b) (4)% w/w glycerin, a sodium citrate (b) (4) (methylparaben and propylparaben), (b) (4) (sucralose), and grape flavor.

In the current resubmission, received 3/18/2019, the applicant proposes to address the deficiencies (b) (4) (b) (4) (b) (4) the applicant proposed revision of the Microbial Limits testing procedure and acceptance criteria by a) (b) (4) (b) (4) b) revision of the acceptance criteria for TAMC and TYMC (b) (4); and c) editorial change to acceptance criteria for *E. coli* and *Burkholderia cepacia* (b) (4) These changes are deemed acceptable from a microbiology perspective. The applicant has performed a risk assessment (b) (4) (b) (4)

The applicant proposes minor changes to the manufacturing process and facilities. The process changes consist (b) (4) (b) (4)

The applicant previously proposed long-term storage of Ozobax at (b) (4) (b) (4) (b) (4) The applicant now proposes refrigerated storage (2°C to 8°C) (b) (4) and a (b) (4)-month shelf life. Based on the stability data provided, (b) (4) (b) (4) (b) (4) the requested shelf life is not supported. Specifically, the (b) (4) the maximum shelf life that can be granted at this time is 12 months. (b) (4) (b) (4)

Facilities

All facilities involved in the manufacture and testing of Baclofen USP and Ozobax® (baclofen) oral solution are currently acceptable.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies:

There are no outstanding deficiencies; however, the comment below should be communicated in the action letter:

Based on the long-term stability data provided, a 12-month expiration dating period is assigned for product stored refrigerated (2°C to 8°C). We remind you that the shelf life should be calculated from the first day of manufacture.

[1] ICH Q1E Evaluation of Stability Data,

Risk Assessment for Baclofen Oral Solution

From Initial Risk Assessment			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Risk Evaluation	
				Second Cycle	Third Cycle
Assay, stability	Formulation, raw materials, container closure, process parameters, scale/equipment	L	(b) (4)	Inadequate; risk to patient is considered high.	Adequate
Physical stability	Formulation, process parameters, moisture	L		Adequate	No change
Dosing accuracy	Dosing device, formulation, process parameters, equipment/scale	M		Adequate	No change
Palatability	Formulation, excipient changes, process parameters	M		Adequate	No change
Microbial limits	Formulation, raw materials, process parameters, moisture	L		Adequate	No change
Leachable, extractables	Formulation, container closure, process parameters	M		Adequate	No change

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate
Section 11 has been edited to add alphabetized excipients, and Section 16 has been edited to add corrected language for USP storage conditions. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Ozobax	Adequate
Established name(s)	Baclofen	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral Solution: 5 mg/ 5 mL	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.	NA	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	5 mg/ 5 mL	Adequate, following DMEPA recommendation to re-state as 5 mL volume
Strength(s) in metric system	mg/mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless solution with a grape aroma.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Ozobax (baclofen)	Adequate
Dosage form(s) and route(s) of administration	Oral solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Citric acid, glycerin, grape flavor, methyl-paraben, propylparaben, purified water, sodium citrate, and sucralose.	Adequate, with list of inactive ingredients added.
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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Antispastic	Adequate
Chemical name, structural formula, molecular weight	4-amino-3-(4-chloro-phenyl)-butanoic acid, $C_{10}H_{12}ClNO_2$, 213.66.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Slightly soluble in water, very slightly soluble in methanol, insoluble in chloroform.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No promotional statements	Adequate

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral solution	Adequate
Strength(s) in metric system	mg/mL	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 473 mL	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, colorless solution with a grape aroma, NDC 69528-301-16	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Dispense in a tight, light-resistant container with a child-resistant closure.	Adequate, following DMEPA recommendation to revise the statement to include a description of the child-resistant closure.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F).	Adequate, following DMEPA recommendation to include refrigeration statement and remove (b) (4) statement.
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: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Child-resistant enclosure.	Adequate, following DMEPA recommendation to include a description of the child-resistant closure.

1.2.4 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 (b) (4) (b) (4) (b) (4) Please notify the prescription drug 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.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured For: Metacel Pharmaceuticals, LLC Athens, GA 30601	Adequate

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

NA

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Proprietary name, established name, and dosage form (font size and prominence	Ozobax (baclofen)	Adequate
Dosage strength	5 mg/5 mL	Adequate, following DMEPA recommendation to state as 5 mg/5 mL
Route of administration	Oral solution	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	473 mL	Adequate
"Rx only" displayed on the principal display	"Rx only" displayed	Adequate
NDC number	69528-301-16	Adequate
Lot number and expiration date	Included.	Adequate, following DMEPA recommendation to indicate location of lot # and expiration date.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 2°C - 8°C (36°F - 46°F).	Adequate, following edit to remove (b) (4) statement.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Name of manufacturer/distributor	Manufactured for Metacel	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
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.	NA	NA
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*

The labels are acceptable following edits made in response to recommendations by CMC and DMEPA to: 1) Remove the (b)(4) statement, 2) include lot number and expiration date, and 3) state dosage strength as 5 mg/5 mL. The labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. The Applicant has made all recommended edits to the container label in response to Information Requests sent by the Agency. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger July 29, 2019

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

Wendy Wilson-Lee July 29, 2019

Dan Berger

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Date: 7/30/2019 02:32:13PM
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Wendy Wilson- Lee

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	**208193**
Assessment Cycle Number	**2nd**
Drug Product Name/ Strength	**Ozobax (baclofen) oral solution, 1 mg/mL**
Route of Administration	**Oral**
Applicant Name	**Metacel Pharmaceuticals, LLC**
Therapeutic Classification/ OND Division	**Orphan Drug, used for multiple sclerosis**
Manufacturing Site	(b) (4)
Method of Sterilization	**Not applicable (non-sterile)**

Assessment Recommendation: **Adequate**

Assessment Summary: **The NDA-Complete Response was submitted in eCTD format. The first product quality microbiology for NDA 208193, originally submitted on 1/11/2016, was reviewed in N208193MR01.docx and found adequate from Microbiology perspective as far as the product is not reformulated and the manufacturing site remains same. A Complete Response Letter was issued for the original submission due to issues with the drug product quality and nonclinical aspects. The applicant has provided updated specification information in the recent CR amendment, which is reviewed below.**

Document(s) Assessed	Date Received
• Complete Response – Resubmission	• 3/18/2019
• Response to Information Request	• 4/1/2019
• Response to Information Request	• 5/29/2019

List Submissions being assessed (table): 3/18/2019, 4/1/2019, 4/16/2019, 5/29/2019

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

Remarks: The applicant has submitted an amendment dated 4/1/2019, which contains a response to the Information Request related to the updated "Stability Summary and Conclusions". The submission dated 4/16/2019 is the response to the Information Request related to the labeling sent on 4/12/2019. The submission dated 5/29/2019 is the response to the Information Request sent on 5/15/2019.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents:

- NDA was reviewed in N208193MR01.doc, dated 10/20/2016 and found adequate.

The drug product Ozobax (Baclofen, 1mg/ml) is an oral solution is indicated for the (b) (4) spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The NDA application was reviewed in N208193MR01.dox, dated 10/20/2016 and found adequate from Microbiology perspective. The applicant has submitted a Complete Response Resubmission on 3/18/2019 and a Response to Information Request on 4/1/2019. The formulation of the drug product and the manufacturing facility is not changed. In the CR response, the applicant has provided information for the new site for the testing of microbial limits and (b) (4) Microbial testing is now performed according to test method number (b) (4) (b) (4) (b) (4) The modification and changes are reviewed below.

P.2.5 Microbiological Attributes

Container/ Closure and Package Integrity – N/A

P.3 MANUFACTURE

(b) (4)

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P.7 CONTAINER CLOSURE

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(3.2.P.8.1/Stability Summery and Conclusion)

Proposed Expiry: (b) (4) Months

The proposed storage condition for Baclofen Oral Solution was (b) (4) (b) (4) (b) (4) The revised long-term stability conditions are 2-8ºC/ambient humidity for 24 months. Stability batches C0412, B0119, and B0121 will be stored under both conditions (b) (4) according to the following schedule.

(b) (4)

<u>Assessment:</u> Adequate

The applicant has set an appropriate proposed expiry for the subject drug product.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

3.2. P.8.2

(b) (4) (b) (4)

(b) (4)

Note to Reviewer: (b) (4)

Post Approval Stability Commitment

Metacel (b) (4) commits to place the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program. Any results falling outside of the approved specifications for the drug product will undergo a detailed investigation and if necessary withdrawn from the market and the deviation will be discussed and resolved with FDA.

Assessment: Adequate

Stability tests and test schedule are adequate to evaluate the microbiological quality of the drug product stored under long-term conditions.

P.8.3 STABILITY DATA

0018 (21) 4/1/2019/3.2.P.8.3/ Stability Data

Stability data was provided for lot numbers C0412 (Attachment #1/ Page: 75-76/287), B0119 and B0121 (Attachment #4/ Page: 85, 91, 95, 100/287). Lot #C0412 was manufactured April 10, 2017 and placed in stability program on May 31, 2017. TAMC, TYMC, *E. coli* and BCC data are provided for the lot# C0412 for the initial and 12 month time points performed (b) (4) for the samples kept at 25±2ºC/ 40% RH and only 12 month time point for samples kept at 2ºC-8ºC/ Ambient RH; in all cases results are conformed. (b) (4)

(b) (4)

Lots #B0119 and #B0121 were manufactured January 18-19, 2018 and placed in stability on February 2, 2018. TAMC, TYMC, *E. coli* and BCC data are provided for the lot# B0119 and B0121 performed (b) (4) for the initial time points for the samples kept at 25±2ºC/ 40% RH; in all cases it conformed. The assay results (b) (4) (b) (4) are provide for initial, 3 month, 6 month, 9 month and 12

month time period at 25±2ºC/ 40% RH and 3 month, 6 month, 9 month, 12 month time period at 2ºC-8ºC/ Ambient RH. In all cases results are conformed.

Assessment: **Adequate**

The stability data support the microbiological quality of the drug product.

MICROBIOLOGY LIST OF DEFICIENCIES - None

Primary Microbiology Assessor Name and Date: Gouri Chattopadhyay, Ph.D., 6/3/2019
Secondary Assessor Name and Date: Elizabeth Bearr, Ph.D., 6/3/2019

Gouri Chattopadhyay

Digitally signed by Gouri Chattopadhyay
Date: 6/03/2019 12:49:58PM
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Elizabeth Bearr

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/s/

MARTHA R HEIMANN
08/22/2019 05:01:45 PM

Recommendation: Complete Response Letter

NDA 208193 Resubmission #16
Review # 2

Drug Name/Dosage Form	Ozobax (Baclofen) Oral Solution
Strength	1 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Metacel Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team, Review #2

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Thomas Wong	ONDP/DNDP1/Branch I
Drug Product	Thomas Wong	ONDP/DNDP1/Branch I
Process	Maotang Zhou	OPF/DPA III/Branch VII
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I
Facility	Derek Smith	OPF/DIA/Branch II
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Walters	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

NDA 208193

SUBMISSIONS REVIEWED (SD #) REVIEW #2	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Quality Response to IR (015)	14-Oct-2016*	Product
Resubmission (015)	02-Jan-2018	Product, Process

* Review deferred from first cycle.

Quality Review Team, Review #1

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Andrei Ponta	ONDP/DNDP1/Branch I
Drug Product	Andrei Ponta	ONDP/DNDP1/Branch I
Process	Sung Kim	OPF/DPA III/Branch VII
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I
Facility	Quallyna Porte	OPF/DIA/Branch II
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED (SD #) REVIEW #2	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA (001)	11-Jan-2016*	All
Labeling/Package Insert (002)	26-Feb-2016	Drug Product
Labeling/SPL Draft (003)	28-Mar-2016	Microbiology
Quality Response to IR (005)	20-May-2016	Drug Product
Quality Response to IR (006)	10-Jun-2016	Microbiology
Quality Response to IR (007)	29-Jun-2016	Process
Quality Response to IR (010)	29-Jul-2016	Drug Product
Quality Response to IR (0012)	11-Aug-2016	Microbiology
Quality Response to IR (013)	16-Sep-2016	Microbiology, Process
Quality Response to IR (014)	07-Oct-2016	Drug Product, Microbiology

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
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	III			Adequate	---	Based on previous reviews
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IND	112300	Baclofen oral solution, bioequivalence study versus generic baclofen tablets manufactured by Ivax (ANDA 72235). The Office of Generic Drugs (OGD) currently designates the Ivax product as the reference listed drug for generic baclofen tablets.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue a Complete Response (CR) letter for NDA 208193, Ozobax® (baclofen) oral solution. From a quality perspective, the application cannot be recommended for approval in its current state.

The outstanding deficiencies identified during review of the January 2, 2018 resubmission relate to (b) (4)

(b) (4)

(b) (4)

II. Summary of Quality Assessments

A. Product Overview

Baclofen was originally developed by Ciba-Geigy (now part of Novartis) for treatment of spasticity resulting from multiple sclerosis. Lioresal® (baclofen) tablets were approved for that indication in 1977, and may also be used for treatment of spasticity resulting from spinal cord injury. Safety and efficacy of baclofen in children under age 12 has not been established. Thus, it is not recommended for use in children. Although Lioresal tablets are no longer marketed, generic 10 mg and 20 mg tablets are available from multiple suppliers.

The applicant proposes marketing of an aqueous oral solution containing baclofen 1 mg/mL for the same indications as approved for baclofen tablets. The oral solution also contains glycerin, citric acid, sucralose, sodium citrate, methylparaben, propylparaben, and grape flavor as inactive ingredients. Approval of the oral solution would (b) (4) The oral solution would also be an age appropriate dosage form for study of baclofen in pediatric patients.

Proposed Indication(s) including Intended Patient Population	Treatment of spasticity resulting from multiple sclerosis or spinal cord injury in patient age 12 years and older
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg given as 20 mg four times daily
Alternative Methods of Administration	Tablets for oral administration (b) (4)

B. Quality Assessment Overview

Drug Substance

The bulk drug substance, Baclofen USP, is manufactured by (b) (4) The applicant cross-references (b) (4) DMF (b) (4) for information regarding manufacture and control of the bulk drug substance. Supporting information for the bulk drug substance was deemed adequate during the first cycle review and remains adequate.

Drug Product

The proposed product, Baclofen oral solution 1 mg/mL is an aqueous solution that contains (b) (4) % w/w glycerin, a sodium citrate (b) (4) (methylparaben and propylparaben), (b) (4) (sucralose), and grape flavor. From a quality perspective, it would normally be considered a relatively low risk product. However, product concerns (b) (4) were noted during the filing review. (b) (4)

(b) (4)

The applicant was advised in the first cycle CR letter to identify the root cause for the (b) (4) issue. The applicant was also advised that if any changes to analytical procedures were made it would be necessary to retest stability samples (if available) or perform new stability studies.

In the resubmission, the applicant accounted for (b) (4)

This approach is not acceptable and the applicant will be required to place additional batches on stability.

Microbiology

All microbiology deficiencies were adequately addressed by the applicant during the first review cycle and the application was deemed acceptable from a Microbiology perspective. The application remains acceptable; however, if the product is reformulated, additional review will be required.

Manufacturing Process

The manufacturing process for Baclofen oral solution submitted in the original NDA consisted of (b) (4)

(b) (4) This change is considered relatively minor and the application is deemed acceptable from a Process perspective.

Facilities

All facilities involved in the manufacture and testing of Baclofen USP and Ozobax® (baclofen) oral solution are currently acceptable. Facility status will be reassessed when the applicant responds to the CR letter

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations at this time. The need for special labeling recommendations should be reassessed based to on the applicant's response to the deficiencies identified in this review.

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies: (see Attachment 2)

Risk Assessment for Baclofen Oral Solution

From Initial Risk Identification			Review Assessment	
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Risk Evaluation at 2nd CR
Assay, Stability	Formulation, raw materials, container closure, process parameters, scale/equipment	L	(b) (4)	Mitigation approaches remain **inadequate** and risk to patient is considered **high**.
Physical stability	Formulation, process parameters, moisture	L		Acceptable
Dosing accuracy	Dosing device, formulation, process parameters, equipment/scale	M		Acceptable
Palatability	Formulation, excipient changes, process parameters	M		Acceptable
Microbial limits	Formulation, raw materials, process parameters, moisture	L		Acceptable
Leachable Extractables	Formulation, container closure, process parameters	M		Acceptable

NDA 208193

ATTACHMENT 2

List of Deficiencies

The following Drug Product deficiencies should be communicated as reasons for a Complete Response.

(b) (4)

It is clearly stated in the January 11, 2017, Complete Response Letter, Item #7, that if the identity, assay, or related substance method has to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated since the current data would not reliable. Therefore, place an additional 2 batches of the drug product on stability per ICH Q1A (R2). Submit sufficient long-term stability data to support the proposed shelf life.

The information requests below are not reasons for a CR, but should addressed in any resubmission.

1. Perform a risk assessment screening (b) (4)

2. Provide batch analysis data on the drug product, batch C0412.

3. Provide reference standard source information (b) (4)

Martha Heimann

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LABELING

There is no change made to the labeling in this NDA resubmission except those items identified in the CR letter dated 1/11/2017.

Below are the items stated in the CR letter:

Item #12 - The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains (b) (4) information, which is not appropriate for the dosage form and strength section. Remove this information.

Response: The applicant revised this section to remove the (b) (4) information from the dosage form and strength section. The labeling in Section 1.14.1 has been updated as shown below:

(b) (4)

Reviewer's Assessment: Adequate

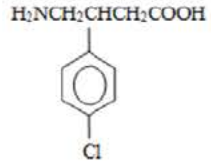
The response is acceptable.

Item #13 - The drug substance structure in the description section is blurry. Update the label with a clear structure.

Response: The package insert was revised to incorporate a structure that is more clear and is provided in Section 1.14.1 as shown below:

11 DESCRIPTION

OZOBAX (baclofen) Oral Solution, is a (b) (4) solution for oral administration. Its chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid, and its structural formula is



$C_{10}H_{12}ClNO_2$

M.W.213.66

Baclofen USP is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

Reviewer's Assessment: Adequate

The response is acceptable.

Item #14 - The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g., color). It also does not have information for in use storage. Update the how supplied section with this information.

Response: The package insert was revised to incorporate the dosage form, strength of the dosage form, and identification of the dosage form in the "How Supplied" section. The data from the In Use Stability Study supports the storage of the product (b) (4) (b) (4) storage conditions. The In-Use Stability Report Revision 1 is provided in Section 3.2.P.8 (Sequence 0010).

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Container labeling:

(b) (4)

Reviewer's Assessment: Inadequate

It is adequate that the response is acceptable. (b) (4)

It is inadequate that (b) (4)

(b) (4)

Review Recommendation: **Inadequate**

The responses to the labeling portion of this resubmission is Adequate. However, the storage condition statement in Section 16 of the PI and the container label is inadequate. The applicant should be notified of this deficiency. Note that this NDA is recommended for Complete Response based on the deficiencies identified in the drug product in this NDA resubmission.

Thomas Wong

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Wendy Wilson- Lee

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/s/

TAURA N HOLMES
05/29/2018

Recommendation: Complete Response Letter

NDA 208193
Review # 1

Drug Name/Dosage Form	Ozobax (Baclofen) Oral Solution
Strength	1 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Metacel Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Andrei Ponta	ONDP/DNDP1/Branch I
Drug Product	Andrei Ponta	ONDP/DNDP1/Branch I
Process	Sung Kim	
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I
Facility	Quallyna Porte	OPF/DIA/Branch II
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

NDA 208193

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA (001)	11-Jan-2016*	All
Labeling/Package Insert (002)	26-Feb-2016	Drug Product
Labeling/SPL Draft (003)	28-Mar-2016	Microbiology
Quality Response to IR (005)	20-May-2016	Drug Product
Quality Response to IR (006)	10-Jun-2016	Microbiology
Quality Response to IR (007)	29-Jun-2016	Process
Quality Response to IR (010)	29-Jul-2016	Drug Product
Quality Response to IR (0012)	11-Aug-2016	Microbiology
Quality Response to IR (013)	16-Sep-2016	Microbiology, Process
Quality Response to IR (014)	07-Oct-2016	Drug Product, Microbiology

* PDUFA Date (11-Jan-2017) is based on receipt of User Fee Cover Sheet on 11-Mar-2016.

Review of the Quality Response to IR dated 14-Oct-2016 (SD # 015) is deferred to the next review cycle.

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	09-Sep-2016	Reviewed by Roger Farr
	III			N/A	N/A	Sufficient information in NDA
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	IV			N/A	N/A	Sufficient information in NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	17851	Innovator application for Lioresal (baclofen) tablets referenced under 505(b)(2) for safety and efficacy. Novartis discontinued marketing of Lioresal tablets, and subsequently withdrew the NDA, for reasons not related to safety or efficacy.
IND	112300	Baclofen oral solution, bioequivalence study versus generic baclofen tablets manufactured by Ivax (ANDA 72235). The Office of Generic Drugs (OGD) currently designates the Ivax product as the reference listed drug for generic baclofen tablets.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue a Complete Response (CR) letter for NDA 208193, Ozobax® (baclofen) oral solution. From a quality perspective, the application cannot be recommended for approval in its current state. Examples of serious deficiencies identified, and not adequately addressed by the applicant during the review include:

- lack of a robust, well-defined, manufacturing process suitable for commercial production,
- product drug stability problems (b) (4)
- failure to demonstrate (b) (4) and
- inadequate validation of analytical procedures used for product release and stability testing.

Given the nature of the outstanding deficiencies there is no assurance that the applicant can manufacture a product that consistently delivers the intended dose. Further, as the applicant (b) (4) have not been identified or evaluated for safety.

II. Summary of Quality Assessments

A. Product Overview

Baclofen was originally developed by Ciba-Geigy (now part of Novartis) for treatment of spasticity resulting from multiple sclerosis. Lioresal® (baclofen) tablets were approved for that indication in 1977, and may also be used for treatment of spasticity resulting from spinal cord injury. Safety and efficacy of baclofen in children under age 12 has not been established. Thus, it is not recommended for use in children. Although Lioresal tablets are no longer marketed, generic 10 mg and 20 mg tablets are available from multiple suppliers.

The applicant proposes marketing of an aqueous oral solution containing baclofen 1 mg/mL for the same indications as approved for baclofen tablets. The oral solution also contains glycerin, citric acid, sucralose, sodium citrate, methylparaben, propylparaben, and grape flavor as inactive ingredients. Approval

of the oral solution would [redacted] The oral solution would also be an age appropriate dosage form for study of baclofen in pediatric patients.

Proposed Indication(s) including Intended Patient Population	Treatment of spasticity resulting from multiple sclerosis or spinal cord injury in patient age 12 years and older
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg given as 20 mg four times daily
Alternative Methods of Administration	Tablets for oral administration [redacted]

B. Quality Assessment Overview

Drug Substance

The bulk drug substance, Baclofen USP, is manufactured by [redacted] The applicant cross-references [redacted] DMF [redacted] for information regarding manufacture and control of the bulk drug substance. Based on a recent review of DMF 18014 to support another application, the DMF is adequate to support approval of this NDA. [Refer to the 9/9/2016 review by R. Farr.]

The applicant provided basic information, including [redacted] the drug substance specification in the NDA. During review of the information submitted to the NDA, minor deficiencies related to the drug substance specification and reporting of impurities [redacted] were identified. These deficiencies are easily correctable and will be communicated separately from the reasons for a CR.

Drug Product

The proposed product, Baclofen oral solution 1 mg/mL is an aqueous solution that contains [redacted]% w/w glycerin, a sodium citrate [redacted] (methylparaben and propylparaben). [redacted] (sucralose), and grape flavor. From a quality perspective, it would normally be considered a relatively low risk product. However, product concerns [redacted]

(b) (4) were noted during the filing review. These concerns were communicated to the applicant in the 74-Day Letter. Based on the applicant's responses to the 74-Day Letter and subsequent follow up information requests (IRs), it has been determined that the applicant did not adequately validate the analytical procedures used in registration stability studies, and proposed for commercial batch release, (b) (4) Thus, (b) (4) the data obtained from registration stability studies are inadequate to inform establishment of a shelf life for the product.

Microbiology

The application, as amended in response to a series information requests, is acceptable from a Microbiology perspective.

In the initial NDA submission, the applicant provided results (b) (4)

The initial NDA submission did not contain the following information:

- Method suitability studies to support use of USP <61> and <62> methods to test for TAMC, TYMC, and absence of *E. coli, Salmonella* species, *S. aureus,* and *P. aeruginosa*
- A detailed description of the test method for *B. cepacia* complex and supporting validation data
- Risk assessment to identify potential sources for introduction of *Burkholderia cepacia* complex organisms (BCC) (b) (4)

The applicant adequately addressed these deficiencies during the review.

Manufacturing Process

The manufacturing process for Baclofen oral solution consists of (b) (4)

(b) (4)

Facilities

All facilities involved in the manufacture and testing of Baclofen USP and Ozobax® (baclofen) oral solution are currently acceptable. Facility status will be reassessed when the applicant responds to the CR letter

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations at this time. The need for special labeling recommendations should be reassessed based to on the applicant's response to the deficiencies identified in this review.

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies: (see Attachment 2)

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(b) (4)

[redacted]

In accordance to 21 CFR 211.166 (b) adequate numbers of batches (first three commercial lots and each year thereafter, a minimum of one lot packaged) will be placed on long term stability at (b) (4) to be tested in line with the approved stability protocol.

Results of the ongoing stability program will be reported in annual reports in accordance with 21 CFR 314.81(b)(2)(viii).

Any results falling outside of the approved specifications for the drug product will undergo a detailed investigation and if necessary withdrawn from the market and the deviation will be discussed and resolved with FDA.

Reviewer's Assessment: Inadequate

The Applicant has committed to placing the first three commercial lots on stability protocol. Yearly thereafter, the Applicant commits to placing one commercial batch to the stability program (b) (4) This is acceptable.

The tests listed in the post-approval protocol are the same tests performed in the stability studies with the exception of (b) (4) The Applicant will be asked to update the post approval stability protocol to include (b) (4) testing.

Note that there are outstanding concerns with assay results on long term stability. Please refer to deficiencies in the above section for additional details.

Deficiency

- (b) (4) *However, the post approval stability protocol does not include* (b) (4) *testing. Update the post approval stability protocol to include* (b) (4) *testing.*

IR Response: Adequate

The Applicant has corrected the stability specifications to specifically state that method (b) (4) includes testing (b) (4) This is acceptable.

R Regional Information

Labeling

1.14 Labeling

Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate***

The package insert contains the proprietary and established name. The dosage form and strength is also present on the label. This is acceptable.

(b) (4)

[redacted]

Reviewer's Assessment: ***Inadequate***

The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, the label contains (b) (4) information which is not appropriate for this section.

(b) (4)

[redacted]

Reviewer's Assessment: ***Inadequate***

The description section contains the proprietary and established name, the dosage form, route of administration, active moiety expression of strength, therapeutic class (may be incorrect), chemical name, structural formula, molecular weight. The structural formula appears to blurry. The Applicant will be asked to update it. It also does not contain excipient information.

(b) (4)

[redacted]

Reviewer's Assessment: ***Inadequate***

The how supplied section does not contain the dosage form, strength, or the identification of dosage form. It also does not have information for in-use storage.

Manufactured by:
Entreprises Importfab, Inc.
50 Hymus Blvd.
Pointe-Claire, QC, Canada H9R 1C9

Manufactured For:
Metacel Pharmaceuticals, LLC
(b) (4)
[redacted]

Reviewer's Assessment: ***Adequate***

This section contains the manufacturer/distributor name. However, it contains the phrase, "manufactured for."

Immediate Container Label

(b) (4)

Reviewer's Assessment: ***Adequate***

The label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, bar code, name of manufacturer, lot number, expiration date, net contents, strength, and the name (proprietary and established).

Carton Labeling: Not Applicable

Reviewer's Assessment: Not applicable

List of Labeling Deficiencies:

1. The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains (b) (4) information which is not appropriate for the dosage form and strength section. Remove this information.
2. The drug substance structure in the description section is blurry. Update the label with a clear structure.
3. The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g. color). It also does not have information for in-use storage. Update the how supplied section with this information.

Environmental Analysis

In accordance with 21 CFR 25.31(a), Metacel Pharmaceuticals, LLC claims a categorical exclusion from the requirement to prepare an Environmental Assessment as the amount of waste to be generated is expected to be small. To our knowledge, no extraordinary circumstances exist.

Baclofen Oral Solution (1 mg/mL) qualifies for a categorical exclusion as the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The claim is supported by performing the calculations indicated under Section III, Part 2, estimating the Concentration of a Substance at the Point of entry into the Aquatic Environment.

EIC – Aquatic (ppb) = A x B x C x D where:

A = Kg/year produced for direct use (as active moiety)

B = 1/Liters per day entering POTWs*

C = year/365 days

D = 109 µg/kg (conversion factor)

*1.321 x 1011 liters per day entering publicly owned treatment works (POTWs), Source: 2000 Needs Survey, Report to Congress

EIC – Aquatic (ppb) = (b) (4) kg/year x 1/1.321 x 1011 liters/day x year/365days x 109 µg/kg

= (b) (4) µg/kg

= (b) (4) ppb

Since the estimated EIC is much lower than 1 ppb, the categorical exclusion is requested.

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

Methods Verification Package - None

Reviewer's Assessment: Not Applicable

Comparability Protocols - None

Reviewer's Assessment: Not Applicable

Post-Approval Commitments

Reviewer's Assessment: Not Applicable

Lifecycle Management Considerations

Reviewer's Assessment: Not Applicable

List of Deficiencies

(b) (4)

[redacted]

(b) (4)

Control of Drug Product (Release and Stability Specifications)

(b) (4)

Drug Product Stability

(b) (4)

(b) (4)

Labeling

1. The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains (b) (4) information which is not appropriate for the dosage form and strength section. Remove this information.
2. The drug substance structure in the description section is blurry. Update the label with a clear structure.
3. The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g. color). It also does not have information for in-use storage. Update the how supplied section with this information.

Primary Drug Product Reviewer Name and Date: Andrei Ponta, Ph.D.14-Nov-2016

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

I concur that the information provided in the NDA is inadequate to assure the identity, purity, strength, and quality of the drug product. I concur with the complete response recommendation.

Wendy I. Wilson-Lee, Ph.D. 14-NOV-2014

Wendy
Wilson- Lee

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Ponta

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MICROBIOLOGY

Product Background:

NDA/ANDA/BLA: 208193

Drug Product Name / Strength: Ozobax™ (baclofen) oral solution

Route of Administration: oral

Applicant Name: Metacel Pharmaceuticals, LLC

Manufacturing Site: (b) (4) (b) (4)

Method of Sterilization: Not applicable (non-sterile)

Review Summary: Recommended for approval.

List Submissions being reviewed: 01/11/2016, 03/28/2016, 06/10/2016, 08/11/2016, 09/16/2016, and 10/07/2016.

Highlight Key Outstanding Issues from Last Cycle: Complete validation of the test for absence of *B. cepacia* requested.

Concise Description Outstanding Issues Remaining: None identified

Supporting/Related Documents: N/A

Remarks Section: The applicant's submission dated 03/28/2016 provides the current version of the drug product labeling. The applicant's submission dated 06/10/2016 is in response to the Agency's information request dated 05/26/2016. The applicant's submission dated 08/11/2016 is in response to the Agency's information request dated 07/28/2016. The applicant's submissions dated 09/16/2016 and 10/07/2016 provide additional information in response to the Agency's information request dated 07/28/2016.

S Drug Substance – Not applicable

P.1 Description of the Composition of the Drug Product

Ozobax™ (baclofen) oral solution, 1 mg/mL, is indicated for (b) (4) spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. It is a clear, colorless, multi-dose, non-sterile, (b) (4) solution, pH (b) (4) The composition of the drug product is: 1.0 mg/mL baclofen USP (API); (b) (4) mg/mL glycerin (b) (4) mg/mL citric acid, anhydrous, (b) (4) mg/mL sodium citrate, dehydrate, (b) (4) mg/mL

sucralose (b) (4) mg/mL methylparaben (b) (4) mg/mL propylparaben (b) (4) mg/mL grape flavor (b) (4) mg/mL (b) (4) Purified Water (b) (4) The package label claims a fill volume of (b) (4) mL and it is packaged in a (b) (4) round amber 16 oz. bottle and closed with a (b) (4) child resistant (b) (4) cap (b) (4) See, eCTD seq #0000: Section 3.2.P.1, Description and Composition of the Drug Product; Section 3.2.P.5.1, Drug Product Specification; Section 3.2.P.7, Summary of Container Closure System; eCTD seq #0003: Section 1.14.1.3, Structured Product Labeling 0003.

Reviewer's Assessment: The applicant provided an adequate description of the drug product's composition and the container closure system.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity – Not applicable.

(b) (4)

P.3 Manufacture

P.3.1 Manufacturers

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(b) (4)

[redacted]

P.7 Container Closure

Summary table of the container closure system proposed – See P.5.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(eCTD seq #0000, Section 3.2.P.2, Pharmaceutical Development Report, pp. 29; Section 3.2.P.5.6, Justification of Specifications)

Proposed Expiry: (b) (4) months

Reviewer's Assessment: The applicant has set an appropriate proposed expiry for the subject drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(b) (4)

See eCTD seq #0000: Section 3.2.P.5.1, Drug Product Specification; Section 3.2.P.8.2, Post Approval Stability Protocol and Commitments.

Section 3.2.P.5.1, Drug Product Specification, and Section 3.2.5.6, Justification of Specifications for Drug Product, (b) (4) conducted during stability testing.

Note to Reviewer: In an Information Request dated 09/12/2016, the Drug Product Reviewer issued the following deficiency:

(b) (4)

Update the post approval stability protocol to include (b) (4) *testing.*

In their response dated 10/07/2016, the applicant corrected the stability protocols for the first 3 commercial lots and for annual lots to specifically state that each include assay (b) (4)

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: (b) (4)

(b) (4)

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: The applicant's Post-Approval Stability Protocol and Commitment are adequate to evaluate the microbiological quality of the subject drug product prior to expiry.

Acceptable

P.8.3 Stability Data

(eCTD seq #0000: Section 3.2.P.8.3, Stability Data for Drug Product)

Stability data was provided for lot numbers K1026, K1027, K1028, and H0816. Lots K1026, K1027, and K1028 met the stability acceptance criteria for TAMC, TYMC, absence of specified organisms. (b) (4) at 24 months. Lot H0816 met the stability acceptance criteria for TAMC, TYMC, absence of specified organisms. (b) (4) at 12 months.

Reviewer's Assessment: The stability data provided by the applicant supports the maintenance of microbiological quality during storage.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable

R Regional Information

Executed Batch Records

The executed batch records provided do not provide information concerning manufacturing processes used to maintain the microbiological quality of the subject drug product.

Reviewer's Assessment: Not applicable.

Comparability Protocols – No CP was included in the application.

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

2.A. Package Insert

The proposed storage conditions for the drug product include a storage temperature (b) (4) (b) (4) and an expiry period of (b) (4) months. See eCTD seq #0000, Section 3.2.P.2, Pharmaceutical Development Report, pp. 29; Section 3.2.P.5.6, Justification of Specifications.

Reviewer's Assessment: The package insert adequately describes the storage conditions for maintenance of the microbiological quality of the subject drug product.

Post-Approval Commitments: N/A

Lifecycle Management Considerations

Reviewer's Assessment: Changes to the post-approval stability protocol would require review.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Elizabeth Bearr, Ph.D., 10/20/2016
Secondary Reviewer Name and Date: Erika Pfeiler, Ph.D.

Erika Pfeiler

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Elizabeth Bearr

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Risk Assessment for Baclofen Oral Solution

From Initial Risk Identification			Review Assessment	
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Risk Evaluation at CR**
Assay, Stability	Formulation, raw materials, container closure, process parameters, scale/equipment	**L**	(b) (4)	Mitigation approaches are **inadequate** and risk to patient is considered **high**.
Physical stability	Formulation, process parameters, moisture	**L**		Acceptable
Dosing accuracy	Dosing device, formulation, process parameters, equipment/scale	**M**		Acceptable
Palatability	Formulation, excipient changes, process parameters	**M**		Acceptable
Microbial limits	Formulation, raw materials, process parameters, moisture	**L**		Acceptable
Leachable Extractables	Formulation, container closure, process parameters	**M**		Acceptable

NDA 208193

ATTACHMENT 2

List of Deficiencies

(b) (4)

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Martha Heimann

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Recommendation: Complete Response Letter

NDA 208193
Review # 1

Drug Name/Dosage Form	Ozobax (Baclofen) Oral Solution
Strength	1 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Metacel Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Andrei Ponta	ONDP/DNDP1/Branch I
Drug Product	Andrei Ponta	ONDP/DNDP1/Branch I
Process	Sung Kim	
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I
Facility	Quallyna Porte	OPF/DIA/Branch II
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

NDA 208193

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA (001)	11-Jan-2016*	All
Labeling/Package Insert (002)	26-Feb-2016	Drug Product
Labeling/SPL Draft (003)	28-Mar-2016	Microbiology
Quality Response to IR (005)	20-May-2016	Drug Product
Quality Response to IR (006)	10-Jun-2016	Microbiology
Quality Response to IR (007)	29-Jun-2016	Process
Quality Response to IR (010)	29-Jul-2016	Drug Product
Quality Response to IR (0012)	11-Aug-2016	Microbiology
Quality Response to IR (013)	16-Sep-2016	Microbiology, Process
Quality Response to IR (014)	07-Oct-2016	Drug Product, Microbiology

* PDUFA Date (11-Jan-2017) is based on receipt of User Fee Cover Sheet on 11-Mar-2016.

Review of the Quality Response to IR dated 14-Oct-2016 (SD # 015) is deferred to the next review cycle.

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	09-Sep-2016	Reviewed by Roger Farr
	III			N/A	N/A	Sufficient information in NDA
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	III			Adequate	---	Based on previous reviews
	IV			N/A	N/A	Sufficient information in NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	17851	Innovator application for Lioresal (baclofen) tablets referenced under 505(b)(2) for safety and efficacy. Novartis discontinued marketing of Lioresal tablets, and subsequently withdrew the NDA, for reasons not related to safety or efficacy.
IND	112300	Baclofen oral solution, bioequivalence study versus generic baclofen tablets manufactured by Ivax (ANDA 72235). The Office of Generic Drugs (OGD) currently designates the Ivax product as the reference listed drug for generic baclofen tablets.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue a Complete Response (CR) letter for NDA 208193, Ozobax® (baclofen) oral solution. From a quality perspective, the application cannot be recommended for approval in its current state. Examples of serious deficiencies identified, and not adequately addressed by the applicant during the review include:

- lack of a robust, well-defined, manufacturing process suitable for commercial production,
- product drug stability problems (b) (4)
- failure to demonstrate (b) (4) and
- inadequate validation of analytical procedures used for product release and stability testing.

Given the nature of the outstanding deficiencies there is no assurance that the applicant can manufacture a product that consistently delivers the intended dose. Further, as the applicant (b) (4) have not been identified or evaluated for safety.

II. Summary of Quality Assessments

A. Product Overview

Baclofen was originally developed by Ciba-Geigy (now part of Novartis) for treatment of spasticity resulting from multiple sclerosis. Lioresal® (baclofen) tablets were approved for that indication in 1977, and may also be used for treatment of spasticity resulting from spinal cord injury. Safety and efficacy of baclofen in children under age 12 has not been established. Thus, it is not recommended for use in children. Although Lioresal tablets are no longer marketed, generic 10 mg and 20 mg tablets are available from multiple suppliers.

The applicant proposes marketing of an aqueous oral solution containing baclofen 1 mg/mL for the same indications as approved for baclofen tablets. The oral solution also contains glycerin, citric acid, sucralose, sodium citrate, methylparaben, propylparaben, and grape flavor as inactive ingredients. Approval

of the oral solution would [redacted] The oral solution would also be an age appropriate dosage form for study of baclofen in pediatric patients.

Proposed Indication(s) including Intended Patient Population	Treatment of spasticity resulting from multiple sclerosis or spinal cord injury in patient age 12 years and older
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg given as 20 mg four times daily
Alternative Methods of Administration	Tablets for oral administration [redacted]

B. Quality Assessment Overview

Drug Substance

The bulk drug substance, Baclofen USP, is manufactured by [redacted] The applicant cross-references [redacted] DMF [redacted] for information regarding manufacture and control of the bulk drug substance. Based on a recent review of DMF 18014 to support another application, the DMF is adequate to support approval of this NDA. [Refer to the 9/9/2016 review by R. Farr.]

The applicant provided basic information, including [redacted] the drug substance specification in the NDA. During review of the information submitted to the NDA, minor deficiencies related to the drug substance specification and reporting of impurities [redacted] were identified. These deficiencies are easily correctable and will be communicated separately from the reasons for a CR.

Drug Product

The proposed product, Baclofen oral solution 1 mg/mL is an aqueous solution that contains [redacted]% w/w glycerin, a sodium citrate [redacted] (methylparaben and propylparaben), [redacted] (sucralose), and grape flavor. From a quality perspective, it would normally be considered a relatively low risk product. However, product concerns [redacted]

(b) (4) were noted during the filing review. These concerns were communicated to the applicant in the 74-Day Letter. Based on the applicant's responses to the 74-Day Letter and subsequent follow up information requests (IRs), it has been determined that the applicant did not adequately validate the analytical procedures used in registration stability studies, and proposed for commercial batch release, (b) (4) Further, in the absence of appropriately validated methods, or identification (b) (4) the data obtained from registration stability studies are inadequate to inform establishment of a shelf life for the product.

Microbiology

The application, as amended in response to a series information requests, is acceptable from a Microbiology perspective.

In the initial NDA submission, the applicant provided results (b) (4)

The initial NDA submission did not contain the following information:

- Method suitability studies to support use of USP <61> and <62> methods to test for TAMC, TYMC, and absence of *E. coli, Salmonella* species, *S. aureus,* and *P. aeruginosa*
- A detailed description of the test method for *B. cepacia* complex and supporting validation data
- Risk assessment to identify potential sources for introduction of *Burkholderia cepacia* complex organisms (BCC) (b) (4)

The applicant adequately addressed these deficiencies during the review.

Manufacturing Process

The manufacturing process for Baclofen oral solution consists of (b) (4)

Facilities

All facilities involved in the manufacture and testing of Baclofen USP and Ozobax® (baclofen) oral solution are currently acceptable. Facility status will be reassessed when the applicant responds to the CR letter

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations at this time. The need for special labeling recommendations should be reassessed based to on the applicant's response to the deficiencies identified in this review.

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies: (see Attachment 2)

Risk Assessment for Baclofen Oral Solution

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Palatability	Formulation, excipient changes, process parameters	**M**		Acceptable
Microbial limits	Formulation, raw materials, process parameters, moisture	**L**		Acceptable
Leachable Extractables	Formulation, container closure, process parameters	**M**		Acceptable

NDA 208193

ATTACHMENT 2

List of Deficiencies

(b) (4)

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Martha Heimann

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