CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215422Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 215422
Review # 1

Drug Product Name	Baclofen
Dosage Form	Oral granules
Strength	5 mg, 10 mg, 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Saol Therapeutics
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	Vicky He	Yong Hu
Microbiology	N/A	N/A
Biopharmaceutics	Swapna Pamu	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

SUBMISSIONS REVIEWED

Submission(s)	Document Date	Discipline(s) Affected
Original NDA	1/22/2021	All
SD-002, Response to IR	3/1/2021	Manufacturing,
SD-005, Response to IR	6/25/2021	Drug product
SD-006, Response to IR	7/12/2021	Biopharmaceutics, manufacturing

Submission(s)	Document Date	Discipline(s) Affected
SD-009, Response to IR	9/1/2021	Drug product
SD-010, Response to IR	9/10/2021	Manufacturing
SD-011, Response to IR	9/10/2021	Drug product
SD-12, Response to IR	9/20/2021	Drug product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	Baclofen USP	Adequate	3/29/2021	F. Burnett
	III		(b) (4)	N/A	--	Information in NDA adequate.

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

Document	Application Number	Description
IND	140719	Development of granule formulation.
NDA	17851	Novartis NDA for Lioresal (baclofen tablets) is referenced under 505(b)(2) to support safety and efficacy of baclofen.

2. CONSULTS

None.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **APPROVAL** of NDA 215422 for Baclofen Oral Granules. From a product quality perspective, the application provides for adequate assurance that the product will be suitable for use by the intended patient population.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Baclofen is a structural analog of γ-aminobutyric acid (GABA) that was initially approved in 1971 (as Lioresal® tablets) for treatment of spasticity resulting from multiple sclerosis. Per labeling, baclofen may also be of some value in patients with spinal cord injuries and other spinal cord diseases. Other approved dosage forms include a parenteral formulation for IT infusion, ODT, and oral solution.

The proposed product is a "stick pack" containing granules, that may be taken directly with or without water, mixed with food, or mixed with liquids for administration via enteral feeding tubes. Three strengths are proposed, 5 mg, 10 mg, and 20 mg.

Proposed indication(s) including intended patient population	Treatment of spasticity resulting from multiple sclerosis. Patients 12 years and older.
Duration of treatment	Chronic
Maximum daily dose	80 mg
Alternative methods of administration	The product may be: • swallowed with or without water, • mixed with soft food, or • mixed with liquid for oral or enteral administration.

B. Quality Assessment Overview

Drug Substance: Adequate

Baclofen USP is manufactured by [redacted] (b) (4) [redacted]. Supporting information for manufacture and control of baclofen is incorporated by cross reference [redacted] (b) (4) DMF [redacted] (b) (4). The DMF was reviewed

and is deemed adequate. (b) (4) assigns a (b) (4) retest period when stored (b) (4).

The NDA includes information on general properties of the drug substance, specifications, and analytical methods. The methods used by (b) (4) and the drug product manufacturer (b) (4) have been shown to be same by comparison.

Drug Product: Adequate

Baclofen Oral Granules consist of white to off white free flowing granules containing baclofen in a 5 mg, 10 mg, or 20 mg single dose packet. The drug product contains compendial excipients, including mannitol, xylitol, saccharin sodium, hypromellose, amino methacrylate copolymer, crospovidone, calcium stearate, colloidal silicon dioxide, and talc. The drug product also contains strawberry flavoring.

The proposed drug product specification includes typical test parameters for a solid oral dosage form. All analytical procedures are adequately described and validated. Related substances are monitored, with an unidentified individual impurity limit of (b) (4)% and specified impurity limits for (b) (4) of (b) (4)%. The individual impurity limit is in line with ICH guidelines. The limit for Related Compound A is consistent with the USP monograph for Baclofen Tablets. oral suspension.

The drug product has been granted a 30-month expiry when stored at controlled room temperature (20°C – 25°C) based on the long-term stability data provided.

Labeling: Adequate

Minor deficiencies have been communicated and will be corrected during final labeling negotiations.

Manufacturing: Adequate

The proposed DP manufacturing process includes (b) (4) The key risk is to content uniformity (CU), which was evaluated to be at medium risk.

Compared to the registration batches, the commercial process has the (b) (4)

[redacted]. The [redacted] will be used for commercial manufacture as for the registration batches, but the [redacted]. Registration batches were made at the commercial DP facility.

The applicant has developed adequate process controls for the [redacted]. Critical process parameters (CPPs) for [redacted]. [redacted] Consistent and acceptable granule uniformity has been demonstrated on the registration batches. CPPs for the commercia [redacted] Registration batch [redacted] results are acceptable and suggested [redacted]. The commercial [redacted]. [redacted] tests include [redacted]. The overall control strategy is acceptable for a medium risk CU product.

All facilities involved in manufacturing or testing of Baclofen USP and Baclofen Oral Granules are currently acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: Adequate

The to-be-marketed formulation was used was used in the relative bioavailability (BA) study comparing to the LD under fasting condition and in food-effect BA studies. In the pivotal BA studies, test product 20 mg was administered with water, without water or with soft food demonstrated bioequivalence to the LD. Thus, formulation bridging is not needed. No biowaiver was requested because all three strengths were studied, and the applicant demonstrated in vivo dose proportionality.

The applicant adopted the dissolution method listed in USP monograph for Baclofen Tablets (500 mL of 0.01 N HCl using Apparatus 2 at 50 rpm). Based on the provided full profile dissolution data from the clinical and registration batches, the selection of the testing conditions and parameters are acceptable. The applicant investigated the discriminatory ability of the proposed dissolution method toward variations in drug substance particle size, excipient levels, and process parameters; however, the discriminatory ability could not be demonstrated. The dissolution method is deemed acceptable given the high solubility of the drug substance and rapid dissolution of the drug product. Based on dissolution profile data for the clinical and registration batches, the applicant's proposed dissolution acceptance criterion of "NLT [redacted]% (Q) at 15 min" is deemed acceptable for quality control of the drug product at batch release and during stability testing.

FDA-approved dissolution method and acceptance criteria for batch release and stability testing of 5 mg, 10 mg and 20 mg of the proposed product:

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II (Paddle)	50	0.01N HCl	500 mL/37°C	Q = (b)(4)% at 15 minutes

Environmental: Adequate

The applicant submitted a claim for categorical under 21 CFR Part 25.31(b). The expected introduction concentration (EIC) for baclofen is less than 1 part per billion and the applicant has included a statement of no extraordinary circumstances.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, Stability	Formulation, container closure, moisture, process parameters	**Low**	(b) (4)	**Adequate**	
Content Uniformity	API physical properties, formulation, process parameters, equipment, scale	**Medium**		**Adequate**	
Physical Stability (solid state)	Formulation, raw materials, process parameters, scale, equipment	**Low**		**Adequate**	
Particle Size	Formulation, raw materials, process parameters, scale, equipment	**Low**		**Adequate**	
Dissolution BCS I/III	API properties, formulation, process parameters, granule size, equipment, scale	**Low**		**Adequate**	
Microbial limits	Formulation, raw materials, moisture, container closure	**Low**		**Adequate**	
Palatability	Formulation, excipient change, process parameters	**Medium**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor, Neurology Products
Office of New Drug Products

10/15/2021

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LABELING

(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	(b) (4) (baclofen) oral granules
Dosage form, route of administration	Oral
Controlled drug substance symbol	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Oral granules: 5 mg, 10 mg, 20 mg baclofen

Is the information accurate? ☐ Yes ☒ No

Revisions identified and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

The Applicant will be asked to revise the established name and the summary of dosage forms and strengths.

2. ***Section 2 Dosage and Administration***

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Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4) (b) (4) The drug product can be administered orally as a mixture with liquids (b) (4) or soft foods, such as apple sauce, yogurt, or pudding. The drug product can also be administered via enteral feeding tubes, such as nasogastric (NG), gastronomy (G), percutaneous endoscopic gastronomy (PEG) and gastrojejunostomy (GJ) tubes. Apple juice or milk (b) (4).

Is the information accurate? ☒ Yes ☐ No

Revisions identified (e.g., change stick pack to packet, addition of feeding tube size range) and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

3. *Section 3 Dosage Forms and Strengths*

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Oral Granules
Strengths: in metric system	5 mg, 10 mg, 20 mg baclofen
Active moiety expression of strength with equivalence statement	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Present

Is the information accurate? ☒ Yes ☐ No

Revisions identified (e.g., change stick pack to packet, including color of granules) and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

4. *Section 11 Description*

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	(b) (4) (baclofen) oral granules
Dosage form and route of administration	Oral
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Present
Statement of being sterile (if applicable)	Present
Pharmacological/ therapeutic class	Present
Chemical name, structural formula, molecular weight	Present
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not Applicable

Is the information accurate? ☒ Yes ☐ No

Revisions identified and will be communicated to the Applicant as part of labeling

negotiations. The PI is adequate assuming Applicant accepts edits.

The Applicant will be asked to correct the structure, reorder the excipients alphabetically, and change stick pack to packet.

5. ***Section 16 How Supplied/Storage and Handling***

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Oral granules: 5 mg, 10 mg, 20 mg baclofen
Available units (e.g., bottles of 100 tablets)	Carton of 90 packets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white (b) (4) granules
Special handling (e.g., protect from light)	Not Applicable
Storage conditions	Controlled Room Temperature (b) (4)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Saol Therapeutics

Is the information accurate? ☒ Yes ☐ No

Revisions (removal of unnecessary information and reorganizing the how supplied section) identified and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

Reviewer's Assessment of Package Insert: ***Inadequate, deficiencies communicated to OND PM***

Prescribing Information complies with regulatory requirements from a CMC perspective; however, some information is absent. Revisions identified and will be communicated to the Applicant as part of labeling negotiations.

II. Labels:

1. ***Container Labels***

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size	Present	Present

and prominence (21 CFR 201.10(g)(2))		
Dosage strength	Present	Present
Net contents	Present	Present
"Rx only" displayed prominently on the main panel	Present	Present
NDC number (21 CFR 207.35(b)(3)(i))	Present	Present
Lot number and expiration date (21 CFR 201.17)	Present	Present
Storage conditions	Present	Present
Bar code (21CFR 201.25)	Present	Present
Name of manufacturer/distributor	Present	Present
And others if space is available	NA	NA

Reviewer's Assessment of Labels: ***Adequate***

The carton/container label complies with regulatory requirements from a CMC perspective. This is acceptable.

Overall Assessment and Recommendation: Adequate pending corrections during labeling negotiations.

Andrei Ponta

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-215422-ORIG-1
Drug Product Name	(b) (4) (baclofen granules)
Dosage Form/ Strength	Granules; 5 mg, 10 mg, 20 mg
Route of Administration	Oral
Applicant Name	Saol Therapeutics Research Limited
Therapeutic Classification/ OND Division	Division of Neurology
Proposed Indication	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.
Submission Date	01/22/2021 (Original)
Primary Reviewer	Swapna Pamu, M.S.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Recommendation	**Adequate**

EXECUTIVE SUMMARY

The Applicant is seeking 505(b)(2) approval for the proposed (b) (4) (baclofen) granules) (in stick packs); 5 mg, 10 mg, 20 mg. (b) (4) is indicated for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The Listed Drug (LD) is LIORESAL® (baclofen) tablets, approved under NDA 017851. The recommended maximum dosage is 80 mg daily (20 mg four times a day), administered orally with or without water. Stick pack contents can be mixed with soft foods for administration within 2 hours. It can also be administered via enteral feeding tubes.

REVIEW SUMMARY:

The Biopharmaceutics review is focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging throughout product development, (3) Biowaiver, and (4) risk assessment. The Applicant did not request Biowaiver because all three strengths have been studied in Phase 1 studies.

(1) Dissolution Method and Acceptance Criterion:

The Applicant adopted the dissolution method listed in USP monograph for Baclofen Tablets (500 mL of 0.01 N HCl using Apparatus 2 at 50 rpm). Based on the provided full profile dissolution data from the clinical and registration batches, the selection of the testing conditions and parameters are acceptable. The Applicant investigated the discriminatory ability of the proposed dissolution method toward the parameters (b) (4)

(b) (4) Additional results were provided for studying drug release with changes in product formulation (b) (4) (b) (4) composition, and process parameter variations (b) (4). Though the discriminatory ability could not be demonstrated, this Reviewer finds it acceptable considering the high solubility of the drug substance and rapid dissolution of the drug product.

Based on the provided full profile dissolution data from the clinical and registration batches, the Applicant's proposed dissolution acceptance criteria of "NLT (b) (4)% (Q) at 15 min" is deemed acceptable for QC testing of the proposed drug product at batch release and during stability testing.

(2) Formulation Bridging:
It is noted that formulation/product bridging is not needed because to-be-marketed formulation/product was used in the relative bioavailability (BA) study comparing to the LD under fasting condition and in food-effect BA studies. In the pivotal BA studies, test product 20 mg was administered with water, without water or with soft food demonstrated bioequivalence to the LD. Formulation composition is proportional between all strengths of the test product and the Applicant demonstrated in-vivo dose proportionality.

(3) Biowaiver:
All three strengths were studied in bioavailability studies. Biowaiver request is not needed or submitted.

(4) Risk Assessment:
Considering the immediate release nature of the drug product and BCS Class III characteristics of baclofen in 0.01N HCl dissolution medium, risk associated with dissolution is low from a Biopharmaceutics standpoint. In addition, time to peak drug concentration (Tmax) of the active moiety is not considered critical regarding treatment effect or safety for the proposed indication.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-215422-ORIG-1 for (b) (4) (baclofen granules), 5 mg, 10 mg and 20 mg, is Adequate.

FDA-approved dissolution method and acceptance criteria for batch release and stability testing of 5 mg, 10 mg and 20 mg of the proposed product:

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II (Paddle)	50	0.01N HCl	500 mL/37°C	Q = (b) (4)% at 15 minutes

BIOPHARAMCEUTICS ASSESSMENT

List Submissions being assessed:

0001, 01/22/2021, Original Submission
0006, 07/12/2021, Response to FDA Information Request

Drug substance & Drug product:
Baclofen granules is a gamma-aminobutyric acid (GABA-ergic) agonist indicated for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. Baclofen granules is provided as a white to off white free flowing granule containing baclofen with a strawberry flavor provided in a stick pack for oral administration. Baclofen drug substance is slightly soluble in water, very slightly soluble in methanol and 96% ethanol, practically insoluble in acetone and insoluble in chloroform. It dissolves in dilute mineral acids and dilute solutions of alkali hydroxides.

BCS DESIGNATION: *A BCS designation is not requested.*

Solubility:
The Applicant claimed that the proposed drug product belongs to the Biopharmaceutics Classification System (BCS) Class III. The provided solubility study results across the physiological pH range (pH 1.2 to 7.4) are summarized below in Table 1, which confirms that baclofen is a highly soluble drug substance, per the BCS criteria. The highest single oral dose 20 mg can be dissolved in 250 ml of medium across physiologic pH range, exhibiting pH dependent solubility (solubility decreased with increasing pH).

Table 1. Baclofen Solubility as a Function of pH

Medium	Solubility [mg/ml]	Dose / Solubility Ratio [ml] for 5 mg	Dose / Solubility Ratio [ml] for 20 mg
pH 1.2[a]	22.3	0.22	0.90
pH 2.0[b]	7.6	0.66	2.63
pH 3.9[c]	9.1	0.55	2.20
pH 4.5[d]	6.1	0.82	3.27
pH 6.8[e]	4.8	1.04	4.17
pH 7.4[f]	4.9	1.02	4.08

[a]0.1 M HCl; [b]0.01 M HCl; [c]phthalate buffer; [d]USP Acetate buffer; [e,f]USP Phosphate buffer

Permeability:
The Applicant stated in the submission that baclofen is a BCS Class III drug but provided no permeability information of the drug substance. However, the available permeability data in Caco-2 cell monolayers for baclofen in the approved N208193 (for Baclofen Oral Solution, 1 mg/mL), i.e., apparent permeability coefficient (Papp) value of 0.876×10^{-7} cm/s, suggest that baclofen belongs to low permeability class.

Dissolution:
The proposed Baclofen granules, 5 mg, 10 mg, 20 mg are very rapidly dissolving (refer to Section 2 below for dissolution profile data and specifications).

DISSOLUTION METHOD AND ACCEPTANCE CRITERIA:
Assessment: *Adequate*

Dissolution Method Development
The proposed dissolution conditions including Apparatus 2, 50 rpm, and 500 mL of 0.01N HCl as dissolution medium are considered acceptable by this Reviewer as the quality control testing for the proposed drug product at batch release and on stability.

The dissolution method development carried out by the Applicant and justifications for using differing dissolution conditions are summarized below[1].

(b) (4)

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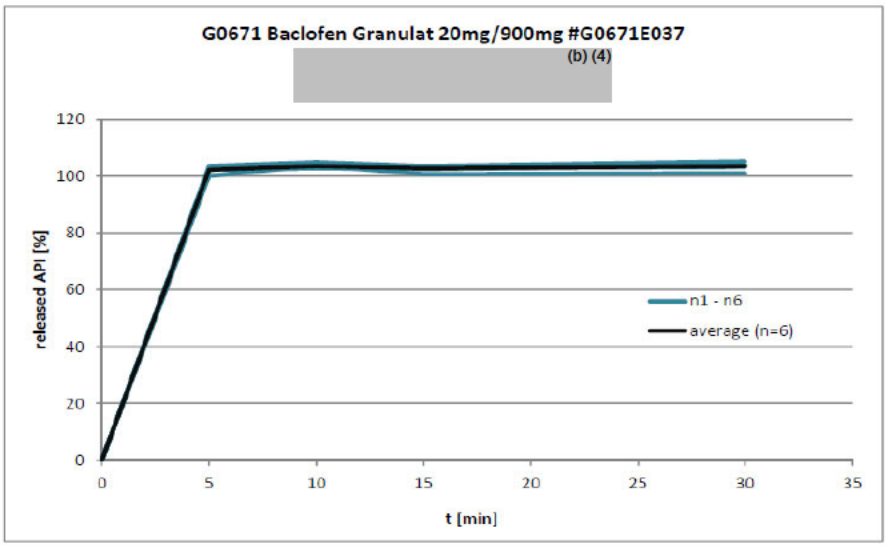
Discriminating Ability of Dissolution Method:
The Applicant investigated the discriminating ability of the proposed dissolution method toward process parameter and API characteristics but not critical quality attributes of the proposed drug product. The performed discriminating ability studies and the results are summarized below.

Table 4. Dissolution of Baclofen from aberrant batch (b) (4) :

Time [min]	Amount of Baclofen released from particular stick pack [%] 1	2	3	4	5	6	Mean	RSD
5	(b) (4)						102.3	1.13
10							103.5	0.74
15							102.7	1.06
30							103.5	1.30

Figure 5. Dissolution of baclofen granules from the aberrant batches, 20 mg



(b) (4)

Note that the dissolution test condition used by the Applicant to conduct this study (b) (4) is different from the proposed method (Apparatus 2, 50 rpm, 500 mL of 0.01 N HCl pH 2.0) (see **Appendix 2** for additional information). In response to Reviewer's information request, the Applicant provided results of studying discriminating ability of the method with changes in product formulation (b) (4) (b) (4), and process parameter variations (b) (4) (b) (4). The resulting dissolution profiles of these intentionally altered batches (i.e., ± 10-20% change to the specification-ranges of these variables; single and multiple changes), though slowed the drug release at early timepoints, are considered similar to target batch and conform to the proposed dissolution acceptance criterion (note that no similarity factor (f2) calculation is necessary because of the very rapid dissolution). Although the method is not found to be discriminatory for the tested

parameter, this Reviewer finds the investigation and findings acceptable due to high solubility of the drug substance and very rapid dissolution of the drug product. Applicant's response is deemed adequate.

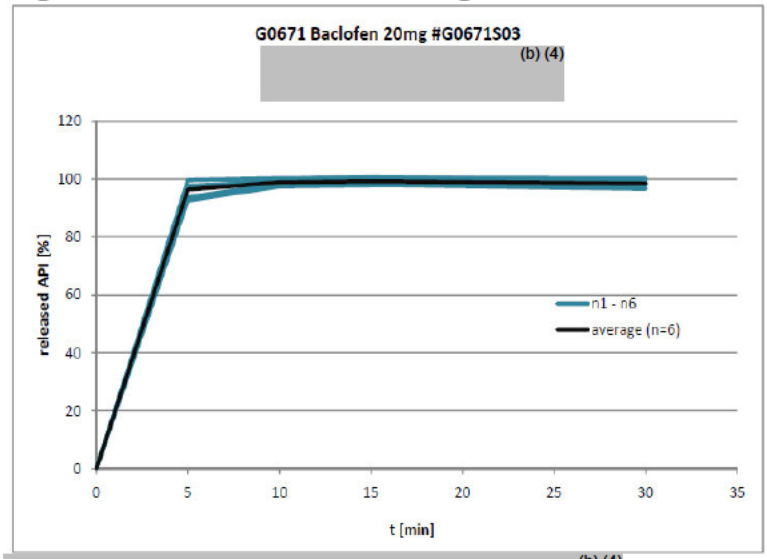
(b) (4)

Baclofen 5 mg oral granules were prepared with (b) (4) The dissolution method that was used by the Applicant to conduct this study (b) (4) is different from the method that is being proposed for the test product for quality control and stability (Apparatus 2, 50 rpm, 500 mL of 0.01 N HCl pH 2.0) (see **Appendix 2** for Information Request).

Table 5. Dissolution of Baclofen from aberrant batch (b) (4)

Time [min]	Amount of Baclofen released from particular stick pack [%] 1	2	3	4	5	6	Mean	RSD
5	(b) (4)						96.4	2.78
10							98.9	1.12
15							99.3	1.17
30							98.5	1.27

Figure 6. Dissolution of baclofen granules from the aberrant batches, 20 mg



(b) (4)

Results of the study (b) (4) showed that the testing condition is not discriminating (b) (4). Although additional data using 50 rpm agitation speed were not provided, this Reviewer finds it acceptable considering the high solubility of

the drug substance and very rapid dissolution of the drug product (completion by 5 min) and does not anticipate improved discriminating ability (b) (4)

Dissolution Acceptance Criterion

Information pertaining to dissolution profiles of the registration or exhibit batches, as well as Information Request for additional data in support of the application (n=12), are provided in **Appendix 1** and **Appendix 2**. Based on the results obtained from dissolution method development studies and dissolution profile data from the biobatch/registration batches (i.e., very rapidly dissolution with near complete drug release of baclofen at the first sampling point, 5 min), the Applicant proposed the acceptance criterion of NLT (b) (4)% (Q) dissolved at 15 minutes for the proposed product. In addition, this Reviewer noted that the drug releases data from all 3 registration batches during the stability testing conform to the proposed acceptance criterion. Therefore, the proposed acceptance criterion of "Q = (b) (4)% in 15 min" is deemed acceptable.

FORMULATION BRIDGING
Assessment: ***Adequate***

Formulation compositions are the same for all strengths, (b) (4) (b) (4) (See Table 8 below). All excipients are within (b) (4) of the total weight of the strengths. Xylitol is included (b) (4) (b) (4) in the formulation (b) (4) (b) (4). The Applicant demonstrated in vivo dose-proportionality among strengths in human subjects, suggesting insignificant impact in absorption/bioavailability by slight differences in formulation composition. In addition, all 3 strengths were shown to have very rapid dissolution, hence additional bridging is not needed.

Table 6. Formulation compositions of 5, 10 and 20 mg

Dose	5 mg		10 mg		20 mg	
Material	**[mg/SD]**	**[%/SD]**	**[mg/SD]**	**[%/SD]**	**[mg/SD]**	**[%/SD]**
Baclofen	5.00	(b) (4)	10.00	(b) (4)	20.00	(b) (4)
Mannitol						(b) (4)
Xylitol						
Saccharin sodium						
Hypromellose						
Amino Methacrylate Copolymer						
Crospovidone						
Calcium stearate						
Colloidal silicon dioxide						
Flavour strawberry						
Talc						
sum						

BIOWAIVER

All three strengths were studied during clinical development (Table 9) - Registration batches 190006609, 190006610 and 190006611 were used in bioavailability studies. Applicant stated that these batches were clinically labelled and assigned the following batch numbers G0671Z001, G0671Z002 and G0671Z003. Registration batches (5 mg & 20 mg) were used in dissolution method development studies. Therefore, biowaiver request is not needed or submitted.

Table 7. Registration batch information

5 mg	Exhibit batch #G0671S036, Registration batch #190006609, 190012688
10 mg	Exhibit batch #G0671S037, Registration batch #190006610, 190012689
20 mg	Exhibit batch #G0671S038, Registration batch #190006611, 190012690

BIOPHARMACEUTICS RISK ASSESSMENT

The Applicant claimed that the proposed drug product belongs to the Biopharmaceutics Classification System (BCS) Class III (high solubility and low permeability). Based on the submitted solubility study results and permeability data from another approved application, this reviewer considers baclofen belongs to BCS Class III. Also considering the immediate release nature of the drug product and high solubility of baclofen in 0.01N HCl dissolution medium, risk in dissolution is low from a Biopharmaceutics standpoint. In addition, time to peak drug concentration (Tmax) of the active ingredients is not considered critical regarding treatment effect or disease control for the proposed indication.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

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GUID: 5ab948e8002c8e63080fe7187098154c

Ta-Chen Wu

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MARTHA R HEIMANN
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