CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215602Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

NDA Number	215602
EDR location	\\CDSESUB1\evsprod\NDA215602\0001
Submission Date	04/05/2021
Submission Type	Original NDA
Regulatory Pathway	505(b)(2)
Product Name	FLEQSUVY™ (baclofen oral suspension)
Dosage Form and Strength	5 mg/mL
Route of Administration	Oral
Proposed Indication	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity in adults and adolescents 12 years of age and older
Applicant	Azurity Pharmaceuticals Inc.
Associated IND	133462
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology-I (DN-I)
OCP Primary Reviewer	Adarsh Gandhi, Ph.D.
OCP Team Leader	Bilal AbuAsal, Ph.D.

Table of Contents

1. Executive Summary

The applicant (Azurity Pharmaceuticals, Inc.) submitted a New Drug Application (NDA) of Baclofen Oral Suspension for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The submission is via the 505(b)(2) pathway using Baclofen Tablets A072235 (held by IVAX/Teva) as the Reference Listed Drug (RLD).

Baclofen Oral Suspension is provided at 5 mg/mL. The proposed dosing regimen of Baclofen Oral Suspension is same as approved Baclofen Tablets: 5 mg TID for three days, 10 mg TID for three days, 15 mg TID for three days, and 20 mg TID for three days. Additional increases may be necessary up to the maximum allowed dosage of 80 mg daily (20 mg QID (four times a day)).

The proposed indication and dosing regimen for the Baclofen Oral Suspension (test) product are the same as the approved RLD (reference) product.

The approval was supported by results from a single pharmacokinetic (PK) study conducted in healthy subjects to demonstrate the bioequivalence (BE) between Baclofen Oral Suspension and RLD as a means to establish a PK bridge between the two formulations. Study RM-05-PK001 was an open-label crossover BE study conducted in adult healthy volunteers with the primary objective of determining the BE between 20 mg Baclofen Oral Suspension (4 mL of 5 mg/mL, i.e., 20 mg final dose) and RLD (baclofen tablets, 20 mg final dose). The BE was established between Baclofen Oral Suspension and RLD formulation at 20 mg single doses where the geometric least squares mean ratio (90% confidence interval) for C_{max} was 99.20 (92.17 – 106.77), AUC_{0-t} was 100.87 (95.29 – 106.77) and $AUC_{0-\infty}$ was 101.91 (96.99 – 107.08) under fasted conditions. Thus, Baclofen Oral Suspension formulation (FLEQSUVY™) was bioequivalent to the RLD (baclofen tablets). This study also evaluated the effect of high-fat meal on PK of Baclofen Oral Suspension, where the high-fat meal decreased AUC by 10% and C_{max} by 33%, which is comparable to the effect of high-fat meal on RLD based on previous ANDA submissions (ANDA 212067, ANDA 074584 and ANDA 211659). The PK study conducted by the applicant provided an adequate scientific bridge for this application to rely on the labeling information of RLD.

A consult request was sent to the Office of Scientific Inspections and Surveillance (OSIS) requesting clinical and bioanalytical site inspections for the BE study RM-05-PK001. The OSIS determined that inspections were previously conducted for other

applications within the surveillance interval, and therefore additional inspections are not warranted at this time (see OSIS memo on DARRTS 07/14/2021).

The focus of this review is to confirm the adequacy of the PK bridge between Baclofen Oral Suspension (FLEQSUVY™) and the reference product (baclofen tablet) and evaluate the dosing instruction with regard to food.

2. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in NDA 215602 and recommends approval based on the bioequivalence demonstrated between Baclofen Oral Suspension (5 mg/mL, final dose 20 mg) to that of the baclofen tablets (20 mg) following a single dose in healthy subjects.

Study results showed a 33% decrease in C_{max} and ~10% decrease in AUC of baclofen when Baclofen Oral Suspension was administered with a standard high-fat meal. This information will be included in section 12.3 of the labeling. However, no specific recommendation will be provided on administering with regard to food, to be consistent with the approved label of RLD.

3. Background and Regulatory History

LIORESAL® (baclofen) Tablets (NDA 020075) was approved by the FDA in 1977 for the alleviation of signs and symptoms of spasticity resulting from MS, spinal cord injuries and other spinal cord diseases, particularly for the relief of flexor spasms and concomitant pain, clonus and muscular rigidity in adults and adolescents 12 years of age and older. LIORESAL® Tablets have been used as the RLD in demonstrating BE to the current RLD, Baclofen Tablets USP (IVAX/Teva ANDA 072235), as well as previously marketed Baclofen Orally Disintegrating Tablets (ODT). Both, LIORESAL® Tablets and the ODT dosage forms have since been discontinued for reasons other than safety or efficacy.

Azurity Pharmaceuticals Inc. developed a Baclofen Oral Suspension (b) (4) that is being evaluated for its comparability to the currently marketed solid oral dosage forms of baclofen.

In summary, the applicant is seeking approval of Baclofen Oral Suspension (FLEQSUVY™) via the 505(b)(2) pathway using baclofen tablets A072235 (held by IVAX/Teva) as the RLD.

The applicant conducted a PK study to demonstrate the BE of Baclofen Oral Suspension to that of the RLD to establish a bridge to demonstrate safety and efficacy.

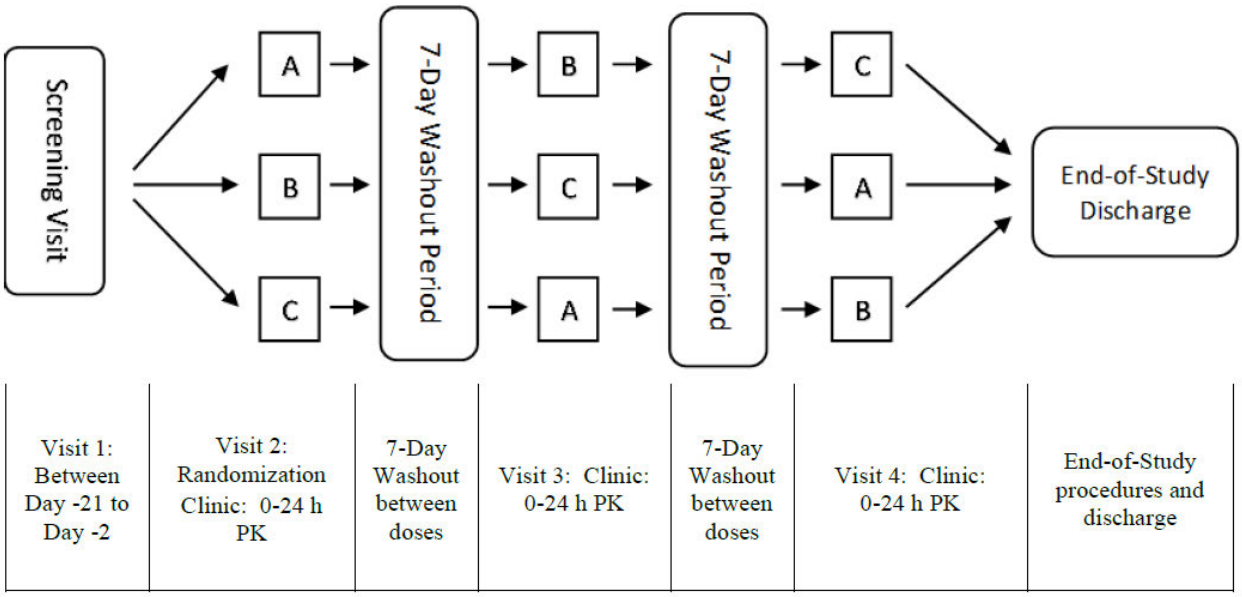
4. Study RM-05-PK001: Pivotal BE and Food Effect study

Title

Randomized, Open-Label, Single-Dose, 3-Way, Relative Bioavailability Study of 20 mg of Baclofen Oral Suspension, 5 mg/mL (4 mL) under Fed and Fasted Conditions and Baclofen Tablets USP, 20 mg under Fasted Conditions in Healthy Adult Subjects

Study Design

This was an open-label, randomized, three-period, crossover design study to evaluate the relative bioavailability of a single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) under fasted versus a single oral dose of Baclofen Tablets, USP (20 mg) under fasted conditions and a single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL under fed conditions in healthy male and female subjects. The study also evaluated the food effect of a single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) under fed and fasted conditions.



Treatment	Treatment Description
A	Test (Fasted): Single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) under fasted conditions
B	Test (Fed): Single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) under fed conditions
C	Reference (Fasted): Single oral dose of Baclofen Tablets, USP (20 mg) under fasted conditions

Each subject was randomized to one of three treatment sequences (ABC, BCA, CAB) with nine subjects per sequence, according to a randomization schedule prepared prior to the start of the study and as displayed below.

Treatment Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B

Primary Objectives

- To determine the relative bioavailability of 20 mg Baclofen Oral Suspension 5 mg/mL (4 mL) and Baclofen Tablet, USP (20 mg) under fasted conditions in healthy adult male and female subjects.
- To assess the effect of food on the absorption of 20 mg Baclofen Oral Suspension 5 mg/mL (4 mL) by administering the formulation under fed versus fasted conditions in healthy adult male and female subjects.

Eligible subjects received a single oral doses of study drug as three study treatments (Treatment A, B or C) on three separate periods in a randomly assigned sequence, with each treatment separated by an approximate 7-day washout period. In each study period (Day 1 of Periods 1, 2 and 3), dosing occurred in the morning after an overnight fast of at least 10 hours. Study drug was administered with 240 mL of room temperature water.

PK Sampling

In each of the three study periods, serial PK blood samples to measure plasma concentrations of baclofen were collected at pre-dose (up to 60 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24 hours post-dose in each period.

High-fat meal Breakfast for Fed Treatment

After an overnight fast of approximately 10 hours, the following high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast was consumed by subjects receiving the test formulation under fed conditions. Subjects began consuming a high-fat meal breakfast approximately 30 minutes prior to dosing and completely consumed the meal approximately 5 minutes prior to dosing. This breakfast contained approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories.

Parameters and Statistical criteria for PK comparison

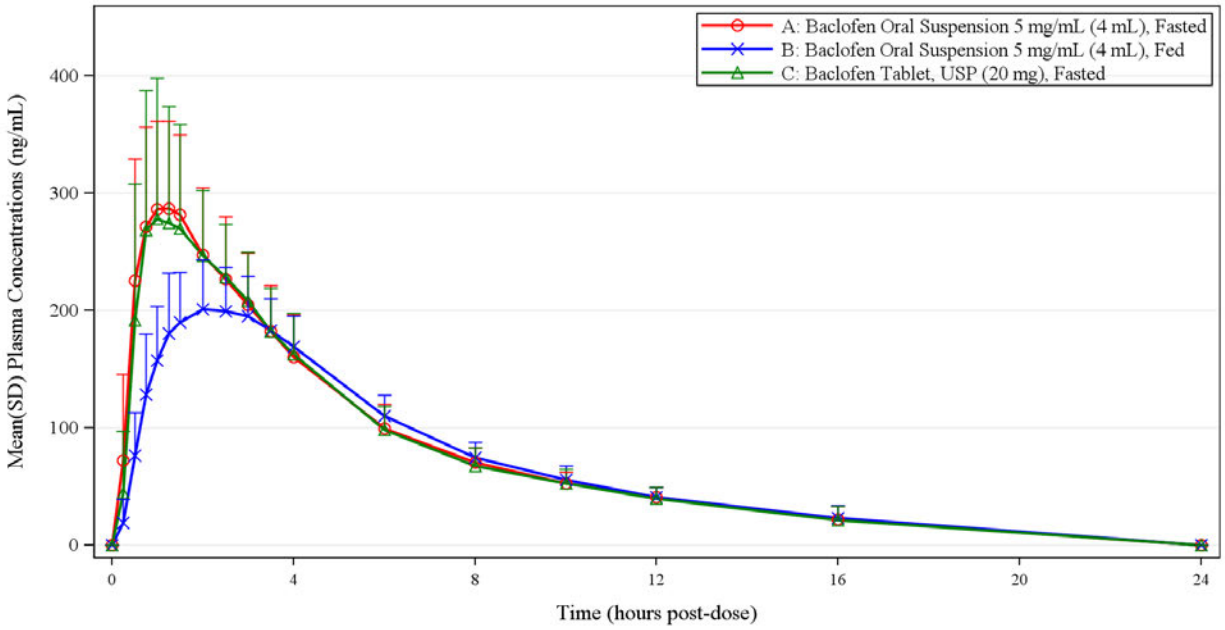
Pharmacokinetic parameters for baclofen including C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} and $t_{1/2}$ were calculated using a non-compartmental analysis method. The relative bioavailability between the Test formulation – 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL) fasted vs. Reference formulation – Baclofen Tablets USP (20 mg), fasted and food effect between 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL), fasted vs. - 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL), fed were considered not significant if the 90% CI for the ratios of geometric means from the ANOVA model of the Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} are within 80.00% to 125.00%.

Results

Out of the 27 subjects enrolled in the study, 27 subjects (100.0%) were included in the PK population, 24 subjects (88.9%) were included in the relative bioavailability population, and 23 subjects (85.2%) were included in the food effect population.

The plot for the mean (±SD) baclofen plasma concentrations for each treatment over the sampling period are presented in **Figure 1**. The descriptive statistics and PK parameters and confidence intervals (CI) of each treatment are shown in **Tables 1, 2 and 3.**

Figure 1: Mean (±SD) Baclofen Plasma Concentration vs. time profile



Source: Clinical study report, Figure 14.2.3.1, Page 79 of 133

The mean baclofen plasma concentration profiles between the suspension formulation (test) and tablet formulation (reference) were similar. The mean peak baclofen plasma concentration profile under fed condition was lower than under fasted condition indicating the absorption of baclofen was affected by food.

Table 1: Summary of Pharmacokinetic Parameters by treatment

Parameter	Statistic	Baclofen Oral Suspension 5mg/mL (4mL) Fasted (N=25)	Baclofen Oral Suspension 5mg/mL (4mL) Fed (N=25)	Baclofen Tablet USP 20 mg Fasted (N=25)
$AUC_{0\text{-}inf}$ (h*ng/mL)	Mean (SD)	1850 (327)	1660 (243)	1800 (349)
$AUC_{0\text{-}t}$ (h*ng/mL)	Mean (SD)	1620 (321)	1460 (222)	1590 (336)
C_{max} (ng/mL)	Mean (SD)	326 (78.0)	216 (36.1)	327 (92.8)
T_{max} (h)	Median (Range)	1.00 (0.50-2.50)	2.00 (1.25-3.50)	1.25 (0.50-3.00)
$t_{1/2}$ (h)	Mean (SD)	5.56 (1.10)	5.29 (1.30)	5.20 (0.838)
K_{el} (1/h)	Mean (SD)	0.130 (0.0292)	0.138 (0.0306)	0.137 (0.0223)

Source: Clinical study report, Table 14.2.2.2, Page 78 of 133. Mean = Arithmetic mean

Similar PK profiles were observed in the oral suspension (Test) and the tablet formulation (Reference). Apparent terminal $t_{1/2}$ (5.56 h) of Baclofen Oral Suspension was also similar to the tablet formulation (5.20 h). Baclofen mean C_{max} for the oral

suspension (326 ng/mL) was similar to the tablet (327 ng/mL). Baclofen mean AUC_{0-t} for the oral suspension (1620 h*ng/mL) was similar to the tablet (1590 h*ng/mL).
The median t_{max} was observed at 1.0 hours for baclofen oral suspension and 1.25 hours for baclofen tablet. The nonparametric test of t_{max} was not statistically significant (p=0.1035), suggesting that there is no difference in the time of peak baclofen concentration for baclofen oral suspension and baclofen tablet.

The median t_{max} was observed at 1.0 hour for baclofen oral suspension administered under the fasted condition and 2.0 hours when administered under the fed condition. The nonparametric test of t_{max} was statistically significant (p=<0.0001), indicating that food does have a delaying effect on the time of peak baclofen concentration.

Table 2: Summary of relative bioavailability analysis for test vs. reference formulations of baclofen under fasted condition.

PK Parameter	Least Squares Geometric Means				Percent Ratio of Geometric Means (%)	Percent Ratio of Geometric Means 90% CI (%)	Intra-Subject CV%
	n	A	n	C	A/C	A/C	
C_{max} (ng/mL)	24	318	24	321	99.20	(92.17 – 106.77)	15.2
AUC_{0-inf} (h*ng/mL)	24	1820	24	1790	101.91	(96.99 – 107.08)	10.2
AUC_{0-t} (h*ng/mL)	24	1590	24	1580	100.87	(95.29 – 106.77)	11.8

Source: Clinical study report, Table 14.2.5.1, Page 91 of 133

With respect to the bioavailability analysis of Treatment A (test under fasted conditions) vs. Treatment C (reference), the 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were contained within the acceptable BE limits (i.e., 80 to 125%).

Table 3: Summary of Food Effect Evaluation of Baclofen Suspension (Test) Formulation (Fed/Fasted)

PK Parameter	Least Squares Geometric Means				Percent Ratio of Geometric Means (%)	Percent Ratio of Geometric Means 90% CI (%)	Intra-Subject CV%
	n	A	n	B	B/A	B/A	
C_{max} (ng/mL)	23	320	23	215	67.04	(62.13 - 72.34)	15.4
AUC_{0-inf} (h*ng/mL)	23	1830	23	1660	90.85	(86.33 - 95.61)	10.3
AUC_{0-t} (h*ng/mL)	23	1600	23	1450	90.62	(85.43 - 96.12)	11.9

Source: Clinical study report, Table 14.2.5.2, Page 92 of 133

The geometric mean percent ratio of Treatment B vs. Treatment A (fed/fasted) AUC_{0-t} in oral suspension was 90.62% (90% CI: 85.43 - 96.12%). C_{max} percent ratio in fed state to fasted state was 67.04% (90% CI: 62.13 - 72.34%). These results indicate a 33% decreased C_{max} and minimum change (9.4%) of AUC_{0-t} was observed when Baclofen Oral Suspension was administered following a high-fat meal.

Dose Proportionality
FLEQSUVY™ is an oral suspension and the BE to the RLD was demonstrated at the highest approved dosage strength. No clinical PK dose strength proportionality studies were conducted; however, PK proportionality can be established based on compositional proportionality.

Conclusions
The reviewer conducted independent analyses, which confirmed the BE of Baclofen Oral Suspension with the RLD (baclofen tablets).

For food effect evaluation, high-fat meal reduced C_{max} by ~33% which was out of the 90% CI specified in BE criteria, however, the ~10% decrease in AUC_{0-t} and $AUC_{0-\infty}$ are not considered significant. Based on the reviewer's cross-study comparison between fed and fasted state for the RLD (baclofen tablets from IVAX Pharmaceuticals) at 20 mg dose from ANDA 074584, administration with standardized high-fat, high-calorie meal led to 29% decrease in C_{max} and 18% decrease in $AUC_{0-\infty}$. The effect of high-fat meal on reference product from the ANDA appears to be comparable with that of Baclofen Oral Suspension in the current submission.

The USPI for the reference product (baclofen tablets) did not include any statement about the dosing instruction with regard to food or the effect of food on baclofen absorption. Without additional evidence to evaluate the clinical significance of reduced C_{max} in presence of food, labeling of baclofen tablets should be in line with the labeling of RLD, thus specific dosage recommendations cannot be made with regard to food.

5. Bioanalytical Method Validation

A validated bioanalytical method BTM-2421-R0 for the determination of baclofen in K2EDTA human plasma by LC-MS/MS was used. Method BTM-2421-R0 is an LC-MS/MS method validated at [redacted] (b) (4) . for the determination of baclofen in K2EDTA human plasma using baclofen-d4 as the internal standard (IS). The final bioanalytical reports [redacted] (b) (4) -R7714 and [redacted] (b) (4) -R7714A1 (addendum) were reviewed. All the data reported in this validation met the method validation acceptance criteria and fulfilled the requirements and recommendations in the FDA Guidance for bioanalytical

method validations for the parameters that were evaluated. Performance characteristics and validation attributes of the bioanalytical method are summarized in **Table 4**.

Table 4: Summary of Bioanalytical Method and Validation Characteristics

Report location		(b) (4)			
Method description		Method BTM-2421-R0 is an LC-MS/MS method for the determination of baclofen in K_2EDTA human plasma using baclofen-d4 as the internal standard (IS). The method used utilized protein precipitation to extract baclofen and the IS from human plasma using methanol. Reversed-phase HPLC separation was achieved with a Phenomenex, Synergi Polar-RP column (50 X 2.0 mm, 4 micron). MS/MS detection was set at mass transitions of m/z 214.1→151.1 for baclofen and m/z 218.1→155.1 for baclofen-d4 (IS) in TIS positive mode.			
Sample volume		25 µL			
Regression		Linear regression			
Weighting factor		$1/x^2$			
Dynamic range		20.0 - 2000 ng/mL			
QC concentrations		20.0 ng/mL (LLOQ), 60.0 ng/mL, 300 ng/mL, 1500 ng/mL, and 15000 ng/mL (Dilution-QC)			
Analyte		Baclofen			
Internal standard		Baclofen-d4			
Linearity		$R^2 \geq 0.9950$			
Lower limit of quantitation (LLOQ)		20.0 ng/mL			
Average recovery of the Analyte (%)		97.3			
Average recovery of the IS (%)		Per BIO-201 guidelines, if a stable isotope labeled IS was used, the recovery established for the unlabeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.			
QC Levels		LLOQ	Low	Mid	High
QC Intra-run precision (%CV)	Run 1	4.7	1.5	1.6	1.3
	Run 2	4.2	2.3	2.9	1.0
	Run 3	3.4	2.8	2.1	1.7
QC Intra-run accuracy	Run 1	-2.5	4.5	-2.7	-2.7
	Run 2	18.0	-5.2	0.0	-5.3

(%Bias)	Run 3	10.0	-8.2	-0.7	-6.7
QC Inter-run precision (%CV)		8.9	6.1	2.4	2.2
QC Inter-run accuracy (%Bias)		8.5	-2.8	-1.0	-5.3
QC sample bench-top stability		17 hours at room temperature			
Stock solution stability		150 days at -20 °C for baclofen stock and spike solutions prepared in diluent (50:50 methanol:water) 20 hours at room temperature for baclofen stock and spike solutions prepared in diluent (50:50 methanol:water)			
Processed sample stability		75 hours at room temperature			
Reinjection reproducibility		85 hours at room temperature			
QC sample freeze/thaw stability		3 freeze (-20 ºC)/thaw (room temperature) cycles			
QC sample long-term storage stability		151 days at -20 °C			
Dilution integrity		15000 ng/mL diluted 10-fold			
Matrix Effect		IS-normalized Matrix factor = 0.99 ± 0.02 at 60.0 ng/mL with %CV = 2.0% IS-normalized Matrix factor = 1.00 ± 0.02 at 1500 ng/mL with %CV = 2.0%			
2% Hemolyzed QC precision range (%CV)		1.5 to 2.9			
2% Hemolyzed QC accuracy range (%Bias)		-7.8 to -6.7			
Blank Selectivity		The selectivity evaluation met the acceptance criteria: no significant baseline interference (≥ 20.0% of the lower limit of quantitation, LLOQ for baclofen or ≥ 5.0% of the IS peak area of the accepted calibration standards and QC samples for the IS) was detected at the retention times of the analyte or the IS in any of the human plasma lots.			
Whole Blood Stability		120 minutes in an ice-water bath (0-4 °C) and 60 minutes at room temperature			
Batch Size		207 samples			
Carryover Evaluation		All of the double blank samples that were evaluated for carryover met the acceptance criteria (analyte peak areas were < 20.0% of the lower limit of quantitation, LLOQ for baclofen and IS peak areas were < 5.0% of the mean IS peak area of the accepted calibration standards and QC samples).			
Interference from Analyte on IS		Not detected at the retention time of IS			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADARSH S GANDHI
01/25/2022 11:49:20 AM

BILAL S ABU ASAL
01/26/2022 09:28:48 PM