CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208193

**MEETING REQUEST-
WRITTEN RESPONSES**

Metacel Pharmaceuticals, LLC
Attention: Jeff Bryant
Chief Operating Officer
137 N. Broad St, Suite E
Winder, GA 30680

Dear Mr. Bryant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for baclofen oral solution 1mg/mL.

We also refer to your submission dated September 20, 2018, containing a meeting request. The purpose of the requested meeting was to obtain additional guidance from the toxicology team and clarification related to the nonclinical deficiencies contained in our June 25, 2018, Complete Response letter.

Further reference is made to our Meeting Granted letter dated October 10, 2018, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your September 20, 2018, background package.

If you have any questions, contact Taura Holmes, PharmD, MS, GWCPM, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: 208193

Product Name: Baclofen oral solution 1mg/mL

Indication: (b) (4)

Sponsor/Applicant Name: Metacel Pharmaceuticals, LLC
Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

The purpose of the meeting is for Metacel Pharmaceuticals, LLC to obtain additional guidance and clarification from the toxicology team regarding the nonclinical deficiencies contained in the Agency's June 25, 2018, Complete Response letter.

2.0 QUESTIONS AND RESPONSES

2.1. Nonclinical

Question 1: The Sponsor proposes (b) (4) as requested in Product Quality Item #1 and Nonclinical deficiencies from the NDA 208193 Complete Response Letter of 06/25/2018. (b) (4) Brief synopses of the studies are [provided in the September 20, 2018, meeting package].

Question 2: The Sponsor proposes (b) (4) Brief synopses of the studies are provided below.

(b) (4)

FDA Response to Questions 1 and 2:
We do not typically provide feedback on the design of standard nonclinical studies; however, we have the following general comments based on the information provided in the briefing document:

(b) (4)

Question 3: The Sponsor proposes (b) (4) . Is this approach acceptable to the Agency?

FDA Response to Question 3:
It is acceptable (b) (4) See response to Questions 1 and 2.

ADDITIONAL COMMENT
We remind you that, when you respond to the June 25, 2018, Complete Response letter, the resubmission must address all deficiencies communicated in the letter.

3.0 PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

5.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that

supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/

ERIC P BASTINGS
12/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 112300

MEETING MINUTES

Codadose, Inc.
Attention: H. Greg Thomas, Ph.D.
2225 Centennial Drive
Gainesville, Georgia 30504

Dear Dr. Thomas:

Please refer to your Pre-Investigational New Drug Application (PIND) file for baclofen oral solution.

We also refer to the teleconference between representatives of your firm and the FDA on September 2, 2011. The purpose of the meeting was to discuss the development of baclofen oral solution (b) (4) for submission as a 505(b)(2) application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Abraham-Burrell, Pharm.D., Regulatory Project Manager at (301) 796-2721.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: September 2, 2011
Meeting Location: teleconference

Application Number: PIND 112300
Product Name: baclofen oral solution
Indication: (b) (4)
Sponsor/Applicant Name: Greg Thomas, Ph.D.

Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Susan Daugherty

FDA ATTENDEES

Division of Neurology Products (DNP)
Russell Katz, M.D., Director
Gerald Podskalny, D.O., Medical Team Leader
Anne Constantino, M.D., Medical Reviewer
Donald C. Thompson Ph.D., Non-clinical Reviewer
Lois Freed, Ph.D., Supervisory Pharmacologist
Susan Daugherty, Regulatory Project Manager

Division of New Drug Quality Assessment I
Martha Heimann, Ph.D., CMC Team Leader
Arzu Selen, Ph.D., Biopharmaceutics Reviewer

Division of Clinical Pharmacology I
Ta-Chen Wu, Ph.D., Clinical Pharmacology Reviewer

Office of Orphan Products
Paras Patel, R.Ph., Senior Regulatory Review Officer

SPONSOR ATTENDEES

CodaDose, Inc.
Jeffery S. Kiel, Ph.D., President
H. Greg Thomas, Ph.D., Vice President
Richard Le Vasseur, Project Manager
(b) (4) Clinical and Regulatory Consultant, (b) (4)
(b) (4) Director Business Development, (b) (4)
(b) (4) Director of Regulatory Affairs, (b) (4)

1.0 BACKGROUND

On March 13, 2011, the Sponsor submitted a pre-IND meeting request to discuss the development of baclofen oral solution (b) (4) for submission as a 505(b)(2) application. Preliminary responses were electronically mailed to the Sponsor on September 1, 2011.

2. DISCUSSION

Regulatory Affairs

Question 8.1-

The proposed regulatory strategy provides for submission of a 505(b)(2) New Drug Application for an oral solution dosage form of baclofen based on the demonstration of safety and effectiveness in NDA 17-851 Lioresal (baclofen) Tablets (b) (4) Is this approach acceptable to the Agency?

Preliminary FDA Response:
A 505(b)(2) application based on the demonstration of safety and effectiveness in NDA 17-851 for Lioresal (baclofen) tablets appears to be an acceptable approach at this time based on the information provided.

(b) (4)

(b) (4) **The Division recommends that Sponsors considering a submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm**

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA- 2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s), you may use a bioequivalent ANDA product as the comparator in a comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on a finding that the drug was not discontinued for reasons of safety or effectiveness.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Discussion at the meeting
The Division clarified that, if the sponsor proposes to rely on the Division's finding of safety and efficacy for the baclofen tablet (Lioresal) NDA, their product could be labeled down to age 12. (b) (4) [redacted] ***The sponsor indicated that they would pursue the same indications that are in the innovator label for baclofen tablets for age 12 and above.***

Question 8.2

(b) (4) Does the Agency agree (b) (4) ?

Preliminary FDA Response:

(b) (4)

There was no discussion of this preliminary response at the meeting.

Chemistry, Manufacturing, and Controls

Question 8.3
The stability studies of the drug product will be performed according to ICH guidelines. What duration of drug product stability data will be required for submission and approval of the NDA?

Preliminary FDA Response:
We recommend that you submit a minimum of 12 months long-term stability data and 6 months accelerated data.

There was no discussion of this preliminary response at the meeting.

Nonclinical Studies

Question 8.4
As the requested indication for baclofen Oral Solution is consistent with the indications for the baclofen tablets, and based on the Agency's previous findings of safety, literature, and the proposed dosing being within the already approved labeling, no nonclinical studies are needed for submission of the baclofen Oral Solution NDA. Does the Agency agree that no additional nonclinical studies will be required for submission of the NDA?

Preliminary FDA Response:

(b) (4)

Discussion at the meeting
The sponsor asked if a juvenile animal study would be needed if the pediatric patient population were limited to those 12 years of age and older. The Division stated that a juvenile animal study would not be needed for that patient population.

Biopharmaceutical and Clinical

Question 8.5
Based on available pharmacokinetic data, solubility of the active ingredient, and same route of administration, the Sponsor requests that FDA waive the requirement for in vivo bioavailability or bioequivalence per 21 CFR 320.22 (b) (3). Does the Agency agree with the request for waiver of the requirement for in vivo bioavailability or bioequivalence?

Preliminary FDA Response:
No. The submitted information does not support the Sponsor's request for a biowaiver. Information and data from a relative bioavailability study comparing the proposed baclofen solution and the tablet are needed. In addition, please clarify your statement that the tablet and the solution formulation should be "considered" bioequivalent. The bioequivalence of baclofen oral solution and the RLD (IR tablet) will need to be established. The PK in pediatric patients below the age of 2 years will need to be evaluated.

We notice that the dosing frequency in the NIH study (i.e., TID) is different from the dosing frequency you propose for baclofen oral solution (i.e., 2-4 divided doses (preferably 4 times per day). The sponsor will need to address how the results of the NIH pediatric PK-PD study can support the proposed dosing regimen for oral solution.

There was no discussion of this preliminary response at the meeting.

Question Number 8.6

(b) (4)

(b) (4)

Preliminary FDA Response:
No. (b) (4)

You must obtain the data and the right of reference to the data for all published (or unpublished) reports from clinical trials and nonclinical studies that you do not own and for information not included in the label of the referenced product(s) that you plan to rely upon in your 505(b)(2) NDA.

There was no discussion of this preliminary response at the meeting.

Question Number 8.7
The Sponsor proposes (b) (4) Does the Agency agree with the proposal to include this indication?

Preliminary FDA Response:
Your proposed indication must be supported by data from adequately designed and well controlled efficacy and safety (including long-term safety) trials in the population you intend to use baclofen oral solution. Your safety and efficacy trials must include (b) (4)

There was no discussion of this preliminary response at the meeting.

Question Number 8.8-
(b) (4) If required, does the Agency agree with the proposed study?

Preliminary FDA Response:

No. (b) (4) [redacted]

There was no discussion of this preliminary response at the meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
09/30/2011