

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209321Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 209321

REFUSAL TO FILE

Jacobus Pharmaceutical Company, Inc.
Attention: Laura R. Jacobus
Vice President & Director of Quality Assurance
37 Cleveland Lane, P.O. Box 5290
Princeton, NJ 08540

Dear Ms. Jacobus:

Please refer to your New Drug Application (NDA) dated December 5, 2017, received December 7, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ruzurgi (3,4-diaminopyridine), 10 mg tablets.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Product Quality

- 1) The NDA does not include supporting information needed for the Agency to assess the adequacy of your chemistry, manufacturing, and controls (CMC) strategy to assure the identity, strength, purity, and quality of the drug substance and drug product. Examples of missing information include, but are not necessarily limited to:
 - a) For the (b) (4) drug substance, you have not provided data to support the process parameters and process controls (b) (4) in the NDA. Specifically, this data should demonstrate (b) (4)
 - b) For the drug product, the application does not contain information to support quality attributes of the product and manufacturing process parameters, for example:
 - i) Data demonstrating splitability of scored tablets at both ends of the proposed hardness range, including content uniformity, friability, dissolution, and stability (90 days). We note that Module 3.2.P.8.1 includes summary information from a tablet splitting study. However, no data were provided and it does not appear, based on the summary information, that splitability was tested at the extremes of the hardness range, or that full stability testing on the split tablets was performed.

ii) Data to support process parameters [REDACTED] (b) (4)

iii) Data to support process parameters [REDACTED] (b) (4)

iv) Information to support acceptance criteria [REDACTED] (b) (4)

Information such as this should be included in sections 3.2.P.2.2 Drug Product and 3.2.P.2.3 Manufacturing Process Development. However, the information provided in the NDA is limited to a brief, qualitative history of the product formulation and a tabulation of changes to the master batch record, including typographical corrections and editorial changes.

- c) Information/data to support in vitro dissolution method development and specification for quality control (QC) and stability testing:
- i) The full dissolution method development report, including complete dissolution data, supporting the selection of the proposed dissolution method (method code DF-DIS-3,4-DAP-2 in M.3.2.P.5.1) evaluating the proposed drug product.
 - ii) Complete multi-point dissolution data [individual (n=12 units), mean, range, SD, % CV] from the pivotal clinical batch(es) and primary registration batches of the commercial formulation in stability testing, for in vitro formulation bridging when it is necessary, as well as for whole tablets vs. mechanically and manually split tablets, generated using the proposed QC dissolution method.
- d) Per 21 CFR §314.50(d)(1)(ii)(b) the application should contain "... for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in 320.38 or 320.63 of this chapter or used to conduct a primary stability study: The batch production record; the specification for each component and for the drug product; the names and addresses of the sources of the active and noncompendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture of the drug product as required by 211.84(d) of this chapter and on the drug product as required by 211.165 of this chapter." The information cited above is required for Lots 16908, 16913, and 16914 (primary stability batches). However, the NDA contains a single tableting batch record (Lot No. 16908) plus packaging records for tablet Lots 16908 and 16914. Although some of the additional information required for Lot No. 16908 may be present in the application, it is not identified, or linked to the batch in any manner.

- 2) The CMC section is disorganized and we are unable to locate information for review without extensive searching through multiple subsections. Even then, the information is not always complete. Examples of poor organization include, but are not necessarily limited to:
- a) Location of analytical procedures and method validation reports. Modules 3.2.S.4.2 and 3.2.S.4.3 should contain a complete description of the analytical procedure including reference standard and sample solution preparation, reagent preparation, equipment parameters, etc., for each test performed on the (b) (4) drug substance and the full method validation report, respectively. Similarly, Module 3.2.P.5 should contain full analytical procedures and method validation reports for the finished tablets. Instead, only summary information is provided. As an example, Module 3.2.S.4.2 contains a one paragraph summary of the drug substance assay method (RM-ASY-3,4-DAP-LC-1), with no link to the full method and Module 3.2.S.4.3 contains only a summary of the method validation results. The full report is incorrectly located in Module 3.2.R and contains the analytical method as a “Draft Method for Validation.”
 - b) It is difficult to locate information pertinent to the proposed commercial product, commercial package configurations, and pivotal development batches (primary stability batches and clinical batches) as this information is intermingled with historical information from the compassionate use program and other information. As an example, in the Stability Summary and Conclusions (Module 3.2.P.8.1), the primary stability batches are not identified, the stability test schedule is not included, and the specific tests performed on stability at each time point are not described. The only way we can determine which tests were performed is by looking at the tabulated stability data.
- 3) The NDA references (b) (4) (b) (4) You should consult with your supplier to ensure that the DMF contains information regarding the manufacturing process and manufacturing process development (b) (4) as the information is not present in the NDA.

Nonclinical

We are unable to locate adequate plasma exposure (C_{max} and AUC) data for either the parent compound or the major human metabolite (3-Ac-DAP) to support the 6-month dietary toxicity study of 3,4-DAP in rat (Study 20049262). The only relevant toxicokinetic data provided were plasma concentrations collected at a single time point on selected days during the dosing period, in the 6-month study and in shorter duration dietary studies in rat.

Although the following issues are not related to our refusal to file this application, you should address these issues if the application is resubmitted.

Labeling

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have the following labeling comments:

Highlights (HL) and Table of Contents (TOC)

1. Please revise the letter height or type size in the HL and TOC to a minimum of 8 points, as required by 21 CFR 201.57(d)(6).
2. The strength is not a component of the product title [see 201.57(a)(2)]; please remove (b) (4)
3. Please add the verbatim statement "Initial U.S. Approval" followed by a placeholder for the four-digit year of approval [see 201.57(a)(3)]. The statement must be placed on the line immediately beneath the established name and should be bolded.
4. Please revise the headings in HL to be centered with respect to the horizontal line [see 201.57(d)(3)].
5. Under the Adverse Reaction heading, please include the criteria used to determine inclusion (e.g., incidence rate) of the most common adverse reactions [see 201.57(a)(11)]. (b) (4)
 can be removed.
6. Under the Contraindications heading, please include all of your proposed contraindications from the Full Prescribing Information (FPI).
7. Use in Specific Populations is an optional heading under HL. If there are no clinically important differences in response or use of the drug in specific populations, the heading can be omitted. Also, (b) (4)
 Please delete this heading and subsequent bullets.

8. The subsection headings in the TOC should be indented and in title case.
9. Please include a horizontal line between the TOC and FPI [see 201.57(d)(2)].

Full Prescribing Information (FPI)

10. To avoid unnecessary clutter in the Indications and Usage statement, it is recommended to only include the tradename. Please remove (b) (4)
11. Please revise all cross-references to be the section title (not subsection), subsection number, and in italics format (including the brackets).
12. To increase clarity and accessibility of information to the reader and to reduce redundancy, please revise the organization of the Dosage and Administration section (e.g., utilize subsections, headings, tables, and/or bullets).
13. In the Dosage Forms and Strengths section, please include the identifying characteristics. As stated in CFR 201.57(c)(4)(ii), this includes the shape, color, coating, scoring, and imprinting, when applicable.
We note you have identified the tablet as scored in the How Supplied/Storage and Handling section. If the drug meets the guidelines and criteria for a scored tablet (see Guidance for Industry: Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation), identify the tablet as “functionally scored.”
14. In the Contraindications section, please include a cross-reference to other sections of the labeling that include a more detailed discussion.
15. In the Adverse Reactions section, only adverse reactions (ARs) as defined in 21 CFR 201.57(c)(7) should be included:
 - For purposes of prescription drug labeling, an AR is an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event (e.g., incidence over control/placebo).
 - Use the term “adverse reactions”; avoid terms such as “adverse events” or “treatment-emergent adverse events”.
16. Please revise the adverse reaction tables to include the listings in order of decreasing frequency per 201.57(c)(7)(ii).
17. Please ensure all table titles (section 6 and 14) are in title case.
18. In the Adverse Reactions section, open-label information can be included if the data identify additional AR information that was not observed during the controlled period; however, (b) (4) Therefore, please remove (b) (4)
19. Drug Interactions (DI) findings with negative results (i.e., no interaction was found) (b) (4) The appropriate location for the DI data is in subsection 12.3. Please remove (b) (4)

20. Under Use in Specific Populations/Lactation (subsection 8.2), the Risk Summary is a required heading that must include:
- The effects of, or a statement of the lack of data for, the drug on the breastfed infant [see 201.57(c)(9)(ii)(A)(2)(ii)]
 - The effects of, or a statement of the lack of data for, the drug on milk production [see 201.57(c)(9)(ii)(A)(2)(iii)]
21. Under the Lactation subsection, please revise the standard statement (i.e., beginning with (b) (4) in your proposed PI) to the current standard risk/benefit statement [see 201.57(c)(9)(ii)(A)(3)]:
- (b) (4)
22. (b) (4)
- Please delete this subsection as these conditions do not apply to your drug.
23. We refer you to 201.57(c)(9)(iv) for the proper required statements in the Pediatric Use subsection. Please ensure that your statement in this subsection is in alignment with the age group you propose in the Indications and Usage section.
24. We refer you to 201.57(c)(9)(v) for the proper required statements in the Geriatric Use subsection, including the required statement if a drug is known to be substantially excreted by the kidney.
25. In the Overdosage section, please include:
- Concentrations of the drug in biologic fluids associated with toxicity or death [see 201.57(c)(11)(iii)]
 - The amount of drug in a single dose that is associated with symptoms of overdose and that is likely to be life-threatening [see 201.57(c)(11)(iv)]
 - Whether the drug is dialyzable [see 201.57(c)(11)(v)]
26. In the Description section, please list the inactive ingredients in alphabetical order as recommended by United States Pharmacopeia (see USP Chapter <1091>).
27. Please see the Guidance, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products —Content and Format (Dec 2016; section C, page 8), which includes a recommendation for a brief introduction at the beginning of the Pharmacokinetics subsection. Content can include:
- PK linearity/non-linearity, prodrug status, or a drug's biopharmaceutics characteristics (e.g., extended-release tablet, orally disintegrating tablet).
 - Exposure, e.g., maximum plasma concentration (C_{max}), area under the plasma drug concentration time curve (AUC)) at the recommended dosage, time to steady state, accumulation ratio following multiple doses, and changes in PK over time if these parameters are informative for clinical use of the drug.
- Information provided in the brief introduction should not be repeated under the headings and subheadings.
28. In the Pharmacokinetics subsection, please remove (b) (4) instead, cross-reference to the appropriate section/subsection that includes this information.

29. If positive findings are discussed in the Clinical Pharmacology section, and a cross-reference to another section is not included, then additional information about the lack of clinical relevance of the information should be included (e.g., there is no clinical significance or the clinical significance of the findings is unknown).
30. In the How Supplied/Storage and Handling section:
- We recommend avoiding the inclusion of statements that are not applicable to the healthcare provider, such as, “Keep out of the reach of children”.
 - Please review your storage temperature information and revise for clarity (e.g., include the recommended storage separately from the range of allowable excursion temperatures). For example, you state (b) (4)
31. In the Patient Counseling Information section, numbered subsections (e.g., 17.1, 17.2) are typically unnecessary and not recommended because the content presented about each topic is generally one or two short statements. Moreover, numbered subsections cause unnecessary length and clutter in both this section and in the TOC. Headings (e.g., title case and underlined) are the preferred method for information separation in this section.
32. Please ensure that your patient labeling statements at the end of HL and at the beginning of section 17 match the type and titles of the patient labeling that you submit. For example, your statement in section 17 states the patient labeling is “Patient Information and Instruction for Use”. However, your submitted patient labeling is titled “Medication Guide” [see CFR 208.1 for scope and purpose] rather than “Patient Information”; and we could not locate the submission of an Instructions for Use. Please use the appropriate statements from the following recommended selections:

Highlights

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (if the product will not have a Medication Guide)
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide (if the product will have a Medication Guide; this statement is to be used even if there is also an Instructions for Use)

Patient Counseling Information Section

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues when you resubmit the NDA. The resubmitted labeling will be used for further labeling

discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, contact Michelle Mathers, Regulatory Project Manager, at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely yours,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

WILLIAM H Dunn
01/31/2018



IND 054313

MEETING MINUTES

Jacobus Pharmaceutical Company, Inc.
Attention: Laura Jacobus
Vice President and Director of Quality Assurance
37 Cleveland Lane
P.O. Box 5290
Princeton, NJ 08540

Dear Ms. Jacobus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 3,4-diaminopyridine.

We also refer to the meeting between representatives of your firm and the FDA on February 17, 2016. The purpose of the meeting was to discuss the chemistry, manufacturing, and controls as well as clinical, statistical, regulatory program to support a New Drug Application for 3,4-diaminopyridine.

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, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 17, 2016, 2:00 p.m. – 3:00 p.m.
Meeting Location: FDA White Oak Campus, Building 22, Room 1311

Application Number: IND 054313
Product Name: 3,4-diaminopyridine
Indication: Treatment of Lambert-Eaton myasthenic syndrome
Sponsor/Applicant Name: Jacobus Pharmaceutical Company, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I

Ellis Unger, MD, Director
Robert Temple, MD, Deputy Director

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nicholas Kozauer, MD, Clinical Team Leader
Ronald Farkas, MD, PhD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Richard Houghtling, PhD, Nonclinical Reviewer
David Hosford, MD, PhD, Medical Officer
Laura Jawidzik, MD, Medical Officer
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Products

Martha Heimann, PhD, Neurology CMC Lead
Katherine Windsor, PhD, Quality Reviewer

Office of Clinical Pharmacology

Xinning Yang, PhD, Clinical Pharmacology Reviewer
Kevin Krudys, PhD, Pharmacometrics Team Leader

Office of Biostatistics

Kun Jin, PhD, Team Leader, Division of Biometrics I
Junshan Qiu, PhD, Statistical Reviewer, Division of Biometrics I

Controlled Substance Staff

Martin Rusinowitz, MD, Senior Medical Officer

Office of Scientific Investigations

Cara Alfaro, PharmD, BCPP, Clinical Analyst, Division of Clinical Compliance Evaluation
(via teleconference)

Office of Surveillance and Epidemiology

Danielle Harris, PharmD, Team Leader, Division of Medication Error Prevention and Analysis
Lolita White, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis
(via teleconference)
Erin Hachey, PharmD, Risk Management Analyst, Division of Risk Management (via
teleconference)

Rare Diseases Program

Jonathan Goldsmith, MD, Associate Director
Kathryn O'Connell, MD, Medical Officer (via teleconference)

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES

Jacobus Pharmaceutical Company, Inc.

David P. Jacobus, MD, President
Laura R. Jacobus, Vice President
Kathy Aleš, MD, Medical Director
Guy A. Schiehser, PhD, Director of Chemistry
Richard W. Pursell, Director of Pharmaceutical Operations
Gavin Heffernan, PhD, Senior Research Chemist

(b) (4)

1.0 BACKGROUND

Jacobus Pharmaceutical Company has been developing 3,4-diaminopyridine (3,4-DAP) for the treatment of Lambert Eaton myasthenic syndrome (LEMS). The sponsor also has a compassionate use program that provides drug to treat patients under expanded access IND applications since 1993.

The sponsor has requested the pre-NDA meeting to obtain feedback from the Agency on its chemistry, manufacturing, and controls as well as clinical, statistical and regulatory program. The purpose of this meeting is to discuss and reach agreement with the Agency on the content and format of the proposed New Drug Application (NDA) for 3,4-DAP.

Summary of Regulatory Background	
December 18, 1990	FDA granted Orphan Designation
October 20, 1997	Jacobus submitted initial IND 054313
June 7, 2001	Teleconference to discuss the sponsor's plan to submit the protocol for a controlled clinical trial
September 7, 2010	Pre-NDA Meeting to discuss the sponsor's development program and the requirements for an NDA application
June 17, 2014	EOP2 (Guidance) meeting
September 19, 2014	FDA granted Fast Track Designation
September 29, 2014	CMC pre-NDA meeting
February 9, 2016	Pre-NDA meeting scheduled

FDA sent Preliminary Comments to Jacobus on February 5, 2016. The meeting was rescheduled from February 9 to February 17, 2016.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: [REDACTED] (b) (4)

[REDACTED] (b) (4)
[REDACTED] current Good Manufacturing Practices (GMP) (Figure 1). The specifications for this material will be contained in the Drug Master File (DMF) that

[REDACTED] (b) (4)

. *Will this be acceptable to the Agency?*

FDA Response to Question 1:

This plan appears acceptable, provided all manufacturing facilities for the drug substance are prepared to manufacture under full cGMPs at the time of NDA submission, as noted in the meeting minutes from the September 29, 2014, pre-NDA CMC meeting.

Meeting Discussion: There was no meeting discussion.

Question 2: GMP Process

[REDACTED] (b) (4)

FDA Response to Question 2:

We expect at least three months of stability data (both accelerated and long-term) in the application for one batch of DS [REDACTED] (b) (4)

[REDACTED]

Evaluation of the stability data will be a review issue.

Meeting Discussion: There was no meeting discussion.

Question 3: Comparability Protocol - Impurities

For the NDA, the plan is to have [REDACTED] (b) (4)

[REDACTED]

acobus would like to file a comparability protocol with the [REDACTED] (b) (4)

NDA to allow [REDACTED]

[REDACTED]

Would a comparability protocol including 3 batches of DS at release plus 3 months

(b) (4)

FDA Response to Question 3:

Your plan to submit a comparability protocol including batch data and 3 months of stability data for each of three batches appears reasonable and may be sufficient to provide for a reduction from a prior approval supplement to a CBE-30 submission. We remind you that agreement on the reporting category for the specified CMC changes will be part of the process of approving the comparability protocol and will consider the provided stability data. If your comparability protocol is approved, the protocol should be referenced in the cover letter of the subsequent supplement.

Meeting Discussion: There was no meeting discussion.

Question 4: Impurities

Question 4a:

The synthesis of 3,4-DAP passes through (b) (4)

(b) (4) An initial AMES test (b) (4) was AMES positive.

This material was prepared (b) (4)

(b) (4) 2 different laboratories. (b) (4)

(b) (4) AMES positive. There are literature data to support this (b) (4)
position.

(b) (4) . *Will this be acceptable to the Agency?*

FDA Response to Question 4a:

(b) (4)

Meeting Discussion: There was no meeting discussion.

Question 4b:

For routine release testing of 3,4-DAP, GMP DS, Jacobus plans on testing all impurities that have been observed (b) (4)



Will this list be sufficient for this DS? (The proposed limits for the identified impurities was changed in Section 5.2.1 to (b)(4) % consistent with ICH Guidelines).

FDA Response to Question 4b:

Your plan to incorporate all impurities that have been observed (b)(4) appears acceptable. However, evaluation of all impurities limits will be a review matter. The QSAR reports to support the proposed (b)(4) should be included in the NDA submission for review.

Meeting Discussion: There was no meeting discussion.

Question 4c:

Jacobus has validated a GC-MS method for the (b)(4) impurities listed in Question 4b. This method has a limit of quantitation for these (b)(4) impurities of (b)(4) ppm, and the limit of detection is (b)(4) ppm. Jacobus will use this GC-MS test for routine release of all lots of 3,4-DAP GMP DS with acceptance criteria of (b)(4) ppm for any (b)(4) impurities detected, consistent with the ICH M7 Guidance for a 3,4-DAP daily dose (b)(4) *Will this be acceptable to the Agency?*

FDA Response to Question 4c:

The use of a validated GC-MS limit test (limit of detection (b)(4) ppm) for routine release of all lots of 3,4-DAP GMP DS with acceptance criteria of \leq (b)(4) ppm for any (b)(4) impurities detected appears acceptable. The validation of this analytical method will be evaluated during NDA review.

Meeting Discussion: There was no meeting discussion.

Question 5: Specifications

Jacobus will include the specification for (1) the incoming (b)(4) (2) the drug substance (3,4-DAP Pure), and (3) the 3,4-DAP, 10 mg Tablet in the briefing package. *Are these specifications acceptable to the Agency?*

FDA Response to Question 5:

The specifications for incoming 3,4-DAP GMP (b) (4) the drug substance (3,4-DAP Pure) appear reasonable, provided particle size acceptance criteria are specified (as you noted) in the latter specification. Final evaluation of specifications will be a review issue. With respect to the drug product specification, the test parameters appear appropriate. Adequacy of the analytical procedures and acceptance criteria will be a review issue.

Meeting Discussion: There was no meeting discussion.

Question 6: (b) (4)

(b) (4)
Would this change be considered a change to alternative equipment of the same design and operating principles reportable in an annual report (under Scale-Up and Post-Approval Changes Guidance for Immediate Release Solid Oral Dosage Forms, November 1995)?

FDA Response to Question 6:

Reporting the proposed change to the (b) (4) by annual report appears reasonable, provided that there are no accompanying changes to the particle size acceptance criteria.

Meeting Discussion: There was no meeting discussion.

CMC General Comment: We note that in your projected submission timeline, the final submission date of the NDA is dependent on DMF submission from the 3,4-DAP GMP (b) (4). We recommend that you wait for Agency acknowledgement of the DMF submission prior to filing your NDA.

2.2. Nonclinical

Jacobus has no questions for the FDA regarding nonclinical aspects of the submission for this pre-NDA Meeting.

Meeting Discussion:

The sponsor asked whether or not safety pharmacology (SP) studies of 3,4-DAP would be needed. The Division stated that SP studies would not be needed because of the extent of previous human experience. In addition, the sponsor stated that the 9-month nonrodent study has been completed. Therefore, chronic toxicity studies of 3,4-DAP in rodent and nonrodent will be available at the time of NDA submission. The sponsor's plan to conduct reproductive and developmental toxicology and carcinogenicity studies post-approval is acceptable, as the Division has previously stated.

2.3. Clinical

Question 7: Mass Balance Study

Jacobus has completed a non-compartmental analysis using urine data collected following administration of 3,4-DAP under fasting and fed conditions in normal volunteers in Study JPC 3,4-DAP.PK1. The median percent recovery for the 20 mg dose under fasting and fed conditions was 90.3% and 85.8%, respectively. The median percent recovery for the 30 mg dose under fasting and fed conditions was 82.6% and 67.1%, respectively. The lower urine recovery at the 30 mg dose under fed condition was consistent with the pharmacokinetic (PK) study results. Compared to administration of 3,4-DAP in the fasting state, administration with food led to a statistically significant effect on plasma 3,4-DAP area under the curve from time 0 to the last measurable concentration (AUC_{0-last}) for the 30 mg dose, but not for the 20 mg dose. The ratio of geometric least squares means for plasma 3,4-DAP AUC_{0-last} for fed/fasting state was 0.77 (ie, a 23% reduction) for the 30 mg dose. *Does the division find that these results are adequate to obviate the need to conduct a mass balance study?*

FDA Response to Question 7:

Based on the information provided in your submission, your proposal to not conduct a mass-balance study appears reasonable. However, a final determination of the acceptability of this approach will be based upon a review of a detailed justification in your NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 8: Compassionate Use Data

Starting in January 1993, Jacobus began providing 3,4-DAP for research and treatment protocols in the United States (US). Since Jacobus became involved with the distribution of DS and of 2700 patient years of experience in the US has accrued.

Approximately 627 patients with LEMS have been referred to the Jacobus compassionate distribution program through 230 Investigator-held Investigational New Drug (IND) applications. Given the ultra-rare nature of LEMs, the majority of the INDs were initiated for the treatment of a single patient. Two institutions in particular, Duke University and the Mayo Clinic, were involved in early clinical research and together have accounted for 30% of the LEMS patients who have been treated with Jacobus 3,4-DAP (93 patients at Mayo, 49 patients at Duke prior to 1998, and 49 patients at Duke since 1998). Of the 436 patients with LEMS who have accessed Jacobus 3,4-DAP through physician-held INDs outside of Duke or Mayo, 148 patients (33.9%) are currently under active treatment with Jacobus 3,4-DAP, and the remaining 288 patients (66%) are known to have discontinued Jacobus 3,4-DAP treatment (due to death, lost to follow-up, or discontinuation). A total of 167 of these LEMS cases (38%) have been associated with cancers. To date, Jacobus has performed detailed data extraction of available medical records for 110 of the 288 patients (38%) who are no longer using Jacobus 3,4-DAP. Due to the nature of the Duke and Mayo patient protections, the clinical information that has been shared with Jacobus for these patients has been largely limited, with the exception

of those patients who were referred to the Jacobus JPC 3,4-DAPPER study (hereafter referred to as DAPPER Study) (3 patients from Duke and 7 patients from Mayo, accounting for 20% of the patients screened for the DAPPER Study).

Therefore, for this NDA submission, Jacobus proposes to address the compassionate use exposure to Jacobus' 3,4-DAP product with the following 4 sources:

- Retrospective data collection and active follow-up, with clinical review, beginning with the diagnosis of LEMS through 1 July 2014 for all 52 patients screened in the DAPPER Study. This data will be provided in the Retrospective Pharmacovigilance (RPV) report and Clinical Data Interchange Standards Consortium (CDISC)-compliant datasets will be included in Module 5.
- RPV review of 110 of the 288 patients (excluding those who received treatment solely from Mayo and Duke) who (1) received at least 1 dose of Jacobus' 3,4-DAP product and (2) are known to no longer be taking 3,4-DAP from Jacobus. The same standardized data collection forms used for the RPV report of the 52 patients screened for the DAPPER Study has been used for this data collection. Summary tables, listings, and CDISC-compliant datasets will be provided for these patients.
- Scanned, redacted medical records for the patients not included among the RPV52 or RPV110 who are known to have had at least one of the following events or belong to one of the following subpopulations:
 - patients with seizures or a history of controlled seizures
 - patients with renal insufficiency
 - patients who became pregnant
 - patients with suicidal ideation, or who attempted or completed suicide
 - pediatric patients

Published studies conducted under Investigator INDs will be summarized based solely on those publications.

The information listed above will supplement the results of the randomized withdrawal study (DAPPER Study) and be used as supportive to the safety of Jacobus' 3,4-DAP product in the NDA submission. ***Does the Agency agree with this approach?***

FDA Response to Question 8:

In order for the Division to provide feedback as to whether the DAPPER study could serve as the single source of efficacy data to support the filing of an NDA for LEMS based on the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*, you should provide a comprehensive presentation of the results of that trial prior to the submission of your NDA. If additional efficacy support is necessary, such support might be available from the published studies with 3,4-DAP in LEMS. However, as discussed at the June 17, 2014, End-of-Phase 2 meeting, these studies would generally require complete protocols, statistical analysis plans, and source data submitted in adequate detail to allow for our reanalysis and confirmation of the results.

We agree that the safety data derived from the compassionate use experience in LEMS that is described in your submission could support the filing of an NDA. However, these data, including the narratives and redacted medical records for patients not in the RPV52 or RPV110 groups, will need to be clearly organized and summarized in the NDA to allow for a detailed review. Patients who experienced cardiac adverse events, such as arrhythmias, should also be included in the list of additional subpopulations not included in the RPV52 or RPV110 groups.

Meeting Discussion:

The sponsor gave a summary of the DAPPER study results, described in a synopsis provided prior to the meeting. It was noted that the study included 7 sites with 52 screened and 32 randomized patients that received from 30 to 100 mg of 3,4-DAP which was tapered off over a 3-day period. The W-SAS secondary efficacy endpoint and multiple ancillary endpoints were described as positive and were reportedly consistent with the positive finding for the 3TUG primary efficacy endpoint.

The Division asked if the statistical analysis plan for secondary and tertiary endpoints was pre-specified. It was unclear in the DAPPER study synopsis if the positive tertiary endpoint results were statistically significant. The sponsor stated that the statistical analysis plan was pre-specified in the DAPPER study protocol and that its statisticians (not in attendance) could provide greater detail.

The Division asked the sponsor to comment on whether patients could have become aware of their treatment group status due to a change in drug-related adverse events, such as paresthesias, during tapering. The sponsor stated that patients generally become accustomed to such effects during treatment. The sponsor did not know if any patients became aware of their treatment group as a result of a change in paresthesias or other side effects during drug tapering.

The Division stated that it is not yet clear if the DAPPER study alone could be sufficient to support the filing of an NDA for 3,4-DAP for the treatment of Lambert-Eaton myasthenic syndrome (LEMS). The Division asked if the sponsor has attempted to obtain the data from previously published efficacy studies of 3,4-DAP in LEMS. The sponsor stated that it has access to the data from Sanders et al. (2000). The sponsor stated that it cannot obtain the data from the McEvoy et al. (1989) or Oh et al. (2009) efficacy studies. The sponsor stated that it has not yet requested the data from the Wirtz et al. (2009) study.

The Division discussed the reasons for needing more than a single study to establish effectiveness, as described in detail in the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*.

The sponsor stated that it will send the full DAPPER study report following the meeting to the Division and asked if raw data should also be sent. The Division replied that it

cannot commit to reviewing the raw data before an NDA submission. The Division will review the DAPPER study report, including a presentation of all efficacy outcomes data, and add a post-meeting note to the minutes to address whether sufficient information appears available to support the effectiveness of 3,4-DAP in LEMS for an NDA submission.

Post-Meeting Addendum

The sponsor submitted the clinical study report (CSR) for the DAPPER study. Following a review of this report, the Division sent the following communication to the sponsor:

“We appreciate your providing us the CSR for the DAPPER trial subsequent to the discussion at the recent February 17, 2016, pre-NDA meeting. We note that during this meeting, you indicated that you would also be able to obtain additional supportive source-level data from at least one of the published clinical trials conducted with 3,4-DAP as part of a future NDA submission. After an initial review of the CSR from the DAPPER trial, we believe that these data, along with supportive source level data from at least the Sanders trial discussed at the meeting, could support an NDA filing for 3,4-DAP in LEMS from an efficacy perspective. Therefore, we would encourage you to begin the process of obtaining these additional data at your earliest convenience.”

Question 9: Renal Impairment

Based on the metabolism, clearance, and excretion of 3,4-DAP and its metabolite established in Study JPC 3,4-DAP.PK1, along with the PK/ pharmacodynamic (PD) information from JPC 3,4-DAPPER, Jacobus believes that caution should be exercised in patients with renal impairment, with a more gradual titration schedule, using lower single dose and total daily dose maxima in moderate or severe renal impairment. Jacobus believes that appropriate dosing recommendations can be made in the labeling for these patients based on the known PK of 3,4-DAP. Information on patients in the compassionate use program with known renal insufficiency will be included in the submission. *Does the Agency agree with this approach and assessment?*

FDA Response to Question 9:

The justification provided to support your proposed labeling for dosing of 3,4-DAP in patients with moderate and severe renal impairment appears inadequate based on the lack of sufficient data/experience in those patients. The single example of a patient with severe renal impairment is inadequate to inform labeling. A study to characterize the effect of renal impairment on the pharmacokinetics of 3,4-DAP and its metabolite may be imposed as a post-marketing requirement (PMR) pending a review of the justification provided in the NDA submission along with an assessment of the benefit/risk profile of the parent drug and its metabolite. Any final labeling language in this regard will also be negotiated based on a review of all the relevant information in your NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 10: Hepatic Impairment

Based on the metabolism, clearance, and excretion of 3,4-DAP and its metabolite established in Study JPC 3,4-DAP.PK1, along with the PK/PD information from the DAPPER Study, Jacobus believes that exposure to 3,4-DAP or its metabolite would not be altered in patients with mild or moderate hepatic impairment. Jacobus believes that appropriate dosing recommendations can be made in the labeling for these patients based on the known PK of 3,4-DAP. *Does the Agency agree with this approach and assessment?*

FDA Response to Question 10:

We do not agree. Your submission did not include any data or justification to support your belief that exposure to 3,4-DAP or its metabolite would not be altered in patients with mild or moderate hepatic impairment. Information to support your proposed labeling for these patients will need to be provided in the complete NDA submission. A study to characterize the effect of hepatic impairment on the pharmacokinetics of 3,4-DAP and its metabolite may be imposed as a PMR pending a review of the justification provided in the NDA submission along with an assessment of the benefit/risk profile of the parent drug and its metabolite. Any final labeling language in this regard will also be negotiated based on a review of all the relevant information in your NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 11: QT Effects and Thorough QT Study

Jacobus collected 12-lead electrocardiograms (ECGs) as part of the PK1 study, and ECGs and echocardiograms were collected as part of the DAPPER Study. In addition, all adverse events (AEs), including all deaths from the compassionate use experience, were reviewed for possible QT and cardiac effects. No evidence of an effect of 3,4-DAP on the QT interval was identified. Accordingly, Jacobus believes that a thorough QT study, if deemed necessary after the Agency's review of the safety data provided in the NDA, can be conducted as a post-approval requirement. *Does the Agency agree with this proposal?*

FDA Response to Question 11:

Given the arrhythmogenic mechanism of action (non-specific voltage dependent potassium channel blocking) of 3,4-DAP and the multiple cardiovascular adverse events reported in the literature for 3,4-DAP, we recommend that a thorough QT study be completed prior to your planned NDA submission. Whether or not this study could be conducted as a PMR will be a matter of review.

Meeting Discussion:

The sponsor asked about the need for a QT study of 3,4-DAP, based on the current data that it believes support the safety of 3,4-DAP with respect to QT prolongation. The Division stated that the sponsor should provide these data, along with justification for

requesting a waiver of the need to conduct a QT study, with the NDA submission. The Division clarified that the lack of a QT study would not be considered a filing issue.

Question 12: Special Populations

Although the DAPPER Study screened a limited population of 52 patients with LEMS (32 randomized), the RPV data as of 01 July 2014 provide the long-term clinical context for these patients in the RPV52 report, and an additional long-term clinical picture is provided for 110 of the 288 patients who died, were lost to follow-up, or discontinued as of that date. Note that the 50 US patients represent over 20% of the active US-based LEMS population in the Jacobus 3,4-DAP compassionate distribution program. In addition, scanned, redacted medical records will be provided for pediatric patients with LEMS and patients with seizures (or a history of controlled seizures), pregnancies, suicides (including suicidal ideation, and attempted and completed suicides), or renal insufficiency who have been identified through active monitoring of the compassionate use program and are not included in RPV52 or RPV110. Jacobus believes that there is a sufficient sample of LEMS patients with malignancies among the RPV52 and RPV110 to support labeling wording for appropriate dosing of these patients.

These sources will provide support for the benefit-risk of Jacobus' 3,4-DAP product in patients with LEMS, including these specific subpopulations. Jacobus believes that there is sufficient information available to include as part of the indicated population:

- (b) (4)
- pediatric patients with LEMS
- patients with seizures or a history of controlled seizures
- renal insufficiency
- pregnancy

Would the Agency consider the inclusion of these populations within Jacobus' 3,4-DAP labeling based on the information Jacobus has proposed to be available in the NDA?

FDA Response to Question 12:

A determination as to how the listed subpopulations of LEMS patients may be described in product labeling is premature and will be a matter of review following your NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 13: Registries and Risk Evaluation and Mitigation Strategy

Jacobus is anticipating that a prospective surveillance Registry would be required for 3,4-DAP after approval. To that end, if 3,4-DAP has an acceptable safety profile, Jacobus proposes to establish such a Registry and communicate risks via product labeling and routine pharmacovigilance as described herein. ***Does the Agency agree with this approach?***

FDA Response to Question 13:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: There was no meeting discussion.

Question 14: Integrated Summary of Efficacy and Integrated Summary of Safety

No pooling of efficacy or safety data are planned for this NDA. Jacobus is planning to address all the requirements of the Integrated Summary of Efficacy and Integrated Summary of Safety within Module 2.7.3 and Module 2.7.4, respectively. A cross-reference for each will be provided in Module 5, Section 5.3.5.3. ***Does the Agency agree with this approach?***

FDA Response to Question 14:

Please see the response to Question 8. The extent to which efficacy data would need to be pooled will depend on the final source(s) of those data that are required to support the filing of an NDA. For safety, however, you should pool data to the degree that is possible and potentially informative. For example, we would like your assessment of the incidence of serious adverse events, such as seizures or cardiac arrhythmia, across all exposed patients that you have knowledge of, even though study designs and dosing regimens differ. In contrast, we would not expect you to attempt to derive incidence rates for common non-serious events from pooled data.

Regarding your plan for ISS and ISE location, please see the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

It is acceptable for a small application with a single study or a number of small studies that sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety serve as the narrative portion of the ISE and ISS, respectively. The ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3).

Meeting Discussion:

The sponsor stated that it accepts the data pooling recommendations. The Division noted that all of the relevant safety data, including medical records and narratives from the special patient subpopulations not included in the DAPPER, RPV52, or RPV100 groups should be presented in a concise and organized manner.

Question 15: Standardized Data Collection Forms and Narratives

All CRFs will be provided as PDF files, organized by study, site, and patient (for DAPPER Study), and standardized data collection forms by patient (for RPV52 and RPV110). ***Does the Division agree?***

FDA Response to Question 15:

Your approach seems reasonable.

Meeting Discussion: There was no meeting discussion.

Question 16:

Jacobus will provide the following site-level data in the NDA in accordance with the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for Center for Drug Evaluation and Research (CDER) Inspection Planning for the DAPPER Study. This data will be provided following the *Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning* (version 1.2). The proposed study data to be included in the NDA, as well as details, will be provided in the briefing document. ***Does the Division have any additional advice or requirements beyond that provided in the Guidance documents?***

FDA Response to Question 16:

Please refer to comments under Office of Scientific Investigations (OSI) Requests.

Meeting Discussion: There was no meeting discussion.

Question 17:

The planned submission format and datasets to be included in the NDA will follow the FDA guidance *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (May 2015). The proposed datasets to be included in the NDA, as well as details regarding format, are detailed in the briefing document. ***Does the Division agree or have any advice on the plan?***

FDA Response to Question 17:

Your approach appears reasonable. Please see the statistical comments below.

Meeting Discussion: There was no meeting discussion.

3.0 FDA ADDITIONAL COMMENTS

STATISTICAL COMMENTS

When you submit the NDA, please include the following as part of the original submission:

- (a) All raw as well as derived variables in .xpt format,
- (b) The SAS programs that produced all efficacy results,
- (c) The SAS programs by means of which the derived variables were produced from the raw variables, and
- (d) The data definition file that explains the source and derivation of variables.

Meeting Discussion: There was no meeting discussion.

ABUSE POTENTIAL ASSESSMENT

There is no information regarding the abuse potential of 3,4-DAP in your Pre-NDA Meeting Background/Briefing Materials.

3,4-DAP is a CNS-active new molecular entity (NME). Thus, it is necessary for 3,4-DAP to undergo a full abuse potential assessment that should be included in your NDA.

Your general approach in assessing the abuse potential of 3,4-DAP as part of your drug development program should follow the outline provided below. Your abuse potential assessment will allow the Agency's determination of the risk of abuse of 3,4-DAP. The FDA draft *Guidance for Industry: Assessment of the Abuse Potential of Drugs* (2010) describes the process of evaluating a drug for abuse potential, which includes the following:

Nonclinical Assessment:

- Chemistry
- Pharmacology
 - i. Safety pharmacology
 - ii. Active metabolites
- Receptor binding evaluations at relevant central nervous system sites
- Self-administration studies in animals
- Drug discrimination studies in animals
- Physical dependence studies in animals

Clinical Assessment:

- Human abuse potential studies (HAPS)*
- Clinical safety and efficacy studies (abuse signals):
 - i. Abuse-related adverse events profile
 - ii. Drug withdrawal symptoms
 - iii. Patient narratives, including those related to suspected abuse, misuse,

- overuse or overdose (intentional or unintentional)
- iv. Drug accountability during trials to include drug lost, stolen, diverted or missing as well as an accounting of participants who withdraw without returning study medication

* HAPS may not be applicable. A recommendation to conduct a human abuse potential study (HAPS) is recommended when there is a signal for abuse in nonclinical studies. This *Guidance for Industry* is found on the Internet at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

If 3,4-DAP produces abuse potential signals that warrant scheduling in the Controlled Substances Act (CSA), you will need to include a proposal for scheduling based on an analysis of the NDA's nonclinical and clinical studies. The studies are described in the draft Guidance for Industry on Assessment of Abuse potential of Drugs (2010).

Meeting Discussion:

Previously unseen information was received from the sponsor on February 12, 2016, regarding its completed but limited abuse potential assessment. This consists primarily of in vitro receptor binding studies and generalizations about previous clinical experience. These were not included in the sponsor's pre-NDA Meeting Background/Briefing Materials dated December 31, 2015, upon which Controlled Substance Staff's (CSS's) initial recommendations were made.

Upon review of the most recent information, CSS recommends the following:

1. The protocol for and data representing affinity and potency of 3, 4-diaminopyridine (3, 4-DAP) was not submitted. A table (Table 1) was reviewed but demonstrates percent inhibition values for in vitro binding and enzyme inhibition data. This is inconclusive. You will need to perform receptor binding studies to determine affinity (K_i) and potency of 3, 4-DAP.
2. Animal behavioral pharmacology studies need to be performed and submitted with the NDA. These include drug discrimination, self-administration, and physical dependence studies that are needed to characterize the discriminatory cues and reinforcing properties of 3, 4-DAP.

CSS is available to review nonclinical abuse-related protocols prior to the initiation of studies. A human abuse potential study (HAPS) will be recommended if there is a signal for abuse in nonclinical studies.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See response and meeting discussion. The Division subsequently held a brief teleconference with the sponsor on March 10, 2016, primarily intended to discuss the post-meeting clinical comment regarding the efficacy data that would be necessary to support an NDA filing. The Division asked the sponsor to provide a timeline for its planned submission activities so that it could better comment on the acceptability and completeness of the NDA package. Based on this information, additional discussion may be required to determine if any agreements for late submission of application components would be necessary. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- As indicated in our preliminary response to Question 13, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.
- In addition, we note that a chemistry pre-submission meeting was held on September 29, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review

resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

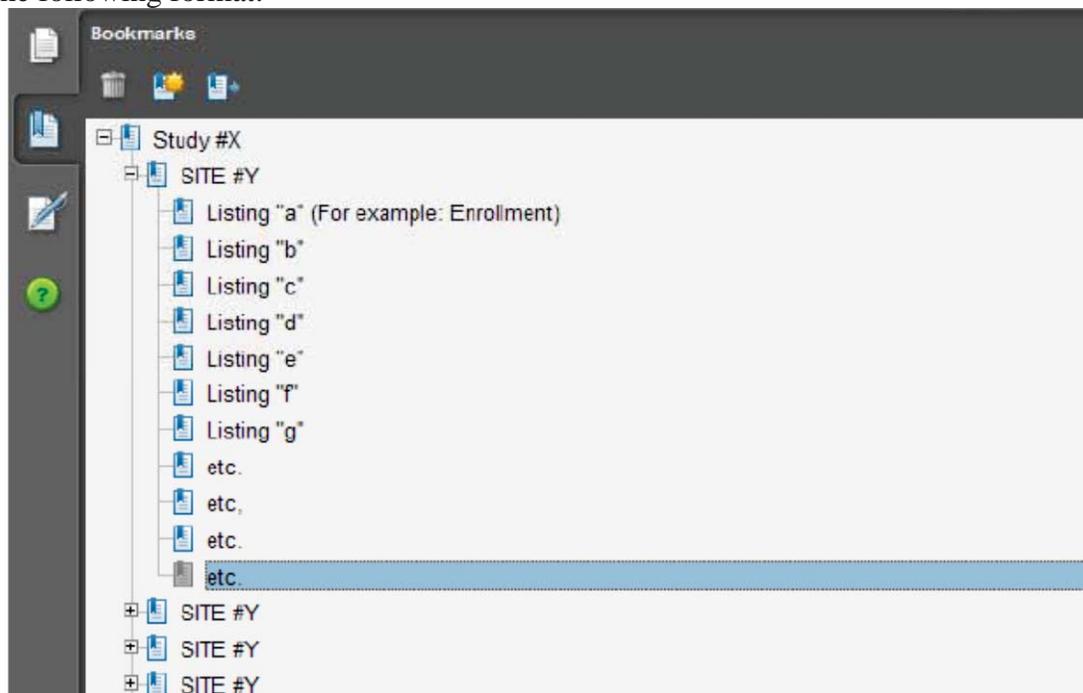
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number

- b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection

Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

“BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor-submitted slide presentation, titled “Pre-NDA Meeting, Type B | 3,4-Diaminopyridine | IND 54313 | February 9, 2016.
- Abuse Potential Assessment: Preclinical Screening – In vitro Receptor Binding Study, received via email on February 12, 2016.

17 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

WILLIAM H Dunn
03/17/2016



IND 054313

MEETING MINUTES

Jacobus Pharmaceutical Company, Inc.
Attention: David P. Jacobus, M.D.
President
37 Cleveland Lane
P.O. Box 5290
Princeton, NJ 08540

Dear Dr. Jacobus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 3,4-diaminopyridine.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2014. The purpose of the meeting was to discuss your overall development program for 3,4-diaminopyridine for the treatment of Lambert-Eaton myasthenic syndrome.

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, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of Phase 2 Meeting

Meeting Date and Time: June 17, 2014 at 11:00 a.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Room 1315

Application Number: IND 054313
Product Name: 3,4-diaminopyridine
Indication: Treatment of Lambert-Eaton myasthenic syndrome
Sponsor/Applicant Name: Jacobus Pharmaceutical Company, Inc.

Meeting Chair: Eric Bastings, MD, Deputy Director
Meeting Recorder: Fannie Choy, RPh, Regulatory Project Manager

FDA ATTENDEES

Center for Drug Evaluation and Research
Robert Temple, MD, Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Andrew Sostek, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Rick Houghtling, PhD, Nonclinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager
Aaron Sherman, Consumer Safety Technician

Office of New Drug Quality Assessment
Martha Heimann, PhD, Neurology CMC Lead
Pei-I Chu, PhD, Quality Reviewer

Office of Clinical Pharmacology
Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Xinning Yang, PhD, Clinical Pharmacology Reviewer

Division of Biometrics I

Kun Jin, PhD, Biometrics Team Leader
Julia Luan, PhD, Statistical Reviewer

SPONSOR ATTENDEES

Jacobus Pharmaceutical Company, Inc.

David P. Jacobus, MD, President
Laura R. Jacobus, Vice President
Kathy L. Aleš, MD, Medical Director
Guy A. Schiehser, PhD, Director of Chemistry
Neil J. Lewis, PhD, Director of Chemical Manufacturing
Gavin Heffernan, PhD, Senior Research Chemist
KaTonna Hibner, Quality Assurance

Haffner Associates

Marlene Haffner, MD

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The text "(b) (4)" is positioned at the top right corner of this redacted area.

1.0 BACKGROUND

Jacobus Pharmaceutical Company has been developing 3,4-diaminopyridine (3,4-DAP) for the treatment of Lambert Eaton myasthenic syndrome (LEMS). The sponsor also has a compassionate use program that provides drug to treat patients under expanded access IND applications since 1993.

Jacobus has requested this meeting to update the Division on the status of the overall development program for 3,4-DAP and to share the topline result of the Phase 2 controlled clinical trial. The sponsor would also like to discuss the components for an NDA application.

Summary of Regulatory Background	
December 18, 1990	FDA granted Orphan Designation
October 20, 1997	Jacobus submitted initial IND 054313
June 7, 2001	Teleconference to discuss the sponsor's plan to submit the protocol for a controlled clinical trial
September 7, 2010	Pre-NDA Meeting to discuss the sponsor's development program and the requirements for an NDA application
June 17, 2014	EOP2 (Guidance) meeting scheduled

2.0 DISCUSSION

Question a:

Will the completed clinical trial satisfy the requirements for marketing authorization if there are statistically significant differences between the withdrawn and the maintained patients?

[FDA Preliminary Response to Question a:](#)

As discussed at the previous type B meeting on September 7, 2010, the short-duration efficacy studies of 3,4-DAP could be used in combination with positive findings on the new study to support NDA filing, with the approval decision remaining a matter of review. The short-duration studies would be of greatest support only if the complete protocols, statistical analysis plans, and source data (including, for example, case report tabulations and case reports forms, as described in CFR 21, 314.50) were submitted in adequate detail to allow re-analysis and confirmation of study findings.

Also, as discussed at the 2010 meeting, the NDA should contain adequate data about the safety of 3,4-DAP after long-term exposure. While you have experience with a large number of patients treated over a number of years, you would have to collect and organize in the NDA the safety data from these patients at a level of detail adequate to support the safety of 3,4-DAP in LEMS.

Safety data from the short-term controlled trials you cite should be submitted in detail, including the complete protocols, case report tabulations and case report forms.

Meeting Discussion:

The sponsor described their recently completed randomized withdrawal study, stating that they remained blinded to the data except for the top-line results, which were positive.

There was discussion about what other data would be needed to support NDA filing. The sponsor described the size and scope of their expanded access safety program, involving about 400 patients over a period of about 20 years. The Division asked the sponsor to do what was feasible to obtain data about the safety of the drug in these patients, with particular focus on serious or potentially serious adverse events like seizure and QTc prolongation which have been posited as potential dose-related adverse effects of the drug. The Division asked the sponsor to schedule a pre-NDA meeting to address any questions that might arise about the expected organization and presentation of the safety and efficacy data in the NDA.

Efficacy data from the previous investigator-conducted efficacy trials were then discussed. The sponsor will do what is feasible to acquire and submit in the NDA the primary data from these studies. The Division requested that biomarker data, such as CMAP, be included in the NDA, stating that positive data on such endpoints would increase the overall persuasiveness of the efficacy data.

Question b:

We have an AMES positive result (b) (4)

We have sent out an additional aliquot for confirmatory testing. EMEA reported this compound AMES negative in the Assessment Report for Zenas (amifampridine), Procedure No. EMEA/H/C/001032 (see page 22 of Attachment 4). We intend to control the level of this impurity according to the ALARP Principle. Do you have any additional comments?

FDA Preliminary Response to Question b:

If the results of the confirmatory assay demonstrate that (b) (4) is mutagenic, the specification limit for this impurity will need to be set at a level appropriate for the proposed duration of dosing in humans (cf., Draft Consensus

Guideline, ICH M7, Step 2 version, February 6, 2013). For chronic administration, the specification limit should be \leq (b) (4) mcg/day.

Meeting Discussion:

The sponsor stated that (b) (4) was positive in the confirmatory Ames assay; therefore, this impurity will be controlled, consistent with acceptable levels for a genotoxic impurity.

Question c:

In regard to the chronic toxicity study, we propose to run three-month rat and dog studies. Given the extensive use in humans would these shorter studies satisfy the requirement? If not, could longer chronic toxicity studies be completed post-approval?

FDA Preliminary Response to Question c:

Toxicity studies of 3 months' duration will not be sufficient to support an NDA for (b) (4). Chronic toxicology studies in two species (26 and 39 weeks in duration in rodent and nonrodent, respectively) will be required at the time of NDA submission.

Meeting Discussion:

1. The sponsor asked for clarification of the need for chronic toxicology studies at the time of the NDA, considering the extent of previous human experience. The Division stated that previous human experience is considered sufficient to allow initiation of Phase 3 clinical trials without completion of the chronic toxicity studies; however, these studies will be required to support an NDA.
2. The sponsor asked for clarification regarding the qualification of the N-acetylated 3,4-DAP metabolite, since there is a species difference in the rate of acetylation of 3,4-DAP in rat (rapid) and dog (slow). The Division noted that this metabolite will be considered qualified if present at sufficient plasma exposures in the appropriate studies, each in a single species (*cf. ICH M3(R2), January 2010; ICH M3(R2) Q & A, June 15, 2011*).

Question d:

What additional clinical and non-clinical studies would be required to be completed prior to marketing authorization rather than as a post-approval commitment (see Section 10, below)?

FDA Preliminary Response to Question d:

Nonclinical

See preliminary response to Question C. Also, it is expected that the dose-ranging study in wild type CB6F1 mouse will be completed at least by the time of NDA submission so that the 6-month study in TgHras2 can be initiated in a timely manner.

The following nonclinical study results may be submitted post-approval, if the available nonclinical and clinical data support such a strategy:

- The 2-year carcinogenicity bioassay in rat and 6-month in TgHras2 mouse.
- A standard battery of reproductive and developmental toxicology studies (cf. ICH M3(R2)).

Meeting Discussion:

Nonclinical

The Division stated that it may not be necessary to conduct multiple subchronic toxicity studies, as proposed by the sponsor. The Division suggested that the sponsor conduct dose range-finding studies of sufficient duration may provide sufficient data upon which to base dose selection for the chronic toxicity studies.

The Sponsor asked about the timing of submission of the chronic toxicology studies and proposed submission of the studies during the NDA review period. The Division stated that submission of the studies during the review period might be acceptable, but would likely result in an extension of the review period.

Post-meeting Discussion

1. We have the following comments regarding your proposed time-line:
 - a. According to the time-line, the nonclinical module would be submitted after the NDA action date; therefore, the proposed estimated submission data for the nonclinical module is not acceptable. The chronic toxicology studies will need to be submitted, at the latest, a few weeks before the action date.
 - b. You should not wait until the report for the 9-month toxicity study in dog is finalized before submitting the rest of the nonclinical data.
 - c. We note that you did not include the dose-ranging study in wild type CB6F1 mouse in the list of nonclinical studies (see preliminary response to Question d).
2. Whatever nonclinical data are available at the time of NDA submission, consisting of the clinical and human pharmacokinetics and bioavailability modules, should be included in the original NDA submission.

Clinical Pharmacology

1. You need to determine the fate and elimination pathway of 3,4-DAP in humans after oral administration. You claim that 3,4-DAP is largely cleared unchanged through urine without providing relevant evidence. In the response to the 2010 meeting package, we recommended that you conduct a mass-balance study. We acknowledge that a renal impairment study is under design. You may consider collecting adequate urine samples from the healthy control group to measure 3,4-DAP and N-acetylated 3,4-DAP. Depending on the results, it may satisfy the aims of a mass-balance study.
2. The *in vitro* studies you have conducted suggest that the majority of the parent drug was metabolized to N-acetylated 3,4-DAP and that major CYP450 enzymes seemed not to be involved. You need to perform further *in vitro* studies to characterize the enzyme responsible for the metabolism of 3,4-DAP. N-acetyltransferase 2 (NAT2) is known to be involved in the N-acetylation metabolism of some drugs. If you confirm that NAT2 is the major enzyme responsible for 3,4-DAP metabolism, you need to characterize the impact of NAT2 status (rapid metabolizers vs. slow metabolizers) on PK and clinical responses of 3,4-DAP. In addition, you may need to balance the numbers of fast metabolizers vs. slow metabolizers of NAT2 in each group of the planned renal impairment study, considering that the status of NAT2 may interfere with the comparisons of PK among different renal function groups.
3. Based on the *in vitro* study, N-acetylated 3,4-DAP seemed to be a major metabolite. You need to determine whether N-acetylated 3,4-DAP is a major metabolite *in vivo*. If it is, you need to determine whether it is an active metabolite. In the planned renal impairment study, we recommend you also measure the plasma concentrations of N-acetylated 3,4-DAP, since it may be predominantly eliminated through the renal route.
4. Please clarify if 3,4-DAP was given with or without food in the efficacy trials. If you propose that 3,4-DAP can be taken regardless of food, you need to conduct a food-effect study to determine the impact of food on the PK of 3,4-DAP.

Meeting Discussion:

Clinical Pharmacology

1. The sponsor stated that urine samples were collected from a completed PK study (JPC 3,4-DAP.PK1) and are under analysis. The sponsor provided some preliminary results verbally during the meeting and will submit the data when the analysis is completed. The sponsor also clarified that there were 4 LEMS patients with mild-to-moderate renal impairment and one patient with severe renal impairment in the efficacy trial, and there seemed to be no significant differences in efficacy and safety results between these subjects and the others. The sponsor asked whether the

information is enough to support labeling rather than conducting a dedicated renal impairment study.

Post-meeting Note: Considering the limited number of LEMS patients with renal impairment in the efficacy trial, we recommend you conduct a dedicated renal impairment study to evaluate the PK of 3,4-DAP and N-acetyl-3,4-DAP. The study does not need to be conducted in patients with LEMS. If you consider such a study unnecessary, please provide a rationale and the proposed labeling language about dosing recommendations for patients with renal impairment.

2. The sponsor acknowledged the Agency's comments and agreed that an *in vitro* study will be conducted. The sponsor also stated that NAT status was identified for 11 patients participating in the efficacy trial with only 1 patient classified as a rapid acetylator. 3,4-DAP was undetectable in this patient after receiving a 10 mg dose, yet there seems no significant difference in efficacy in this patient compared to others. The sponsor further mentioned that the dosing of 3,4-DAP was titrated based on clinical response and about half of the patients received 60 mg/day of 3,4-DAP and 30% patients received 80 mg/day. Thus, the sponsor did not consider information about NAT status is useful for dosing recommendations. The Division clarified that the information about NAT status is still considered useful, e.g., for assessing different titration schemes or establishing a highest recommended dose. In the pre-NDA submission, the sponsor should try to provide as much available NAT status information as they can. The Division also pointed that the proportion of rapid acetylators identified in the sponsor's efficacy trial seemed significantly lower than anticipated from known prevalence in the general population. For example, in Caucasians, rapid metabolizers represent approximately 50% of the population.

Post-meeting note: The difference in the proportion of rapid acetylation metabolizers appears due to the differences in definition. Based on a reference paper you provided (Hein DW and Doll MA, *Pharmacogenomics* (2012) 13(1), 31–41), it seems that you separate the rapid metabolizers we referred to into intermediate acetylators and rapid acetylators.

3. The sponsor clarified that N-acetyl-3,4-DAP is a major metabolite based on Study JPC 3,4-DAP.PK2 and it seems not to be an active metabolite based on preliminary results from a mouse neuromuscular junction study. The Division further asked about the off-target effects of N-acetyl-3,4-DAP and recommended the sponsor conduct an *in vitro* binding study for a panel of receptors. The sponsor agreed to investigate more by conducting *in vitro* studies.
4. The sponsor clarified that there was no restriction on food intake during the efficacy trial. Some patients were administered the drug 3 times a day while some subjects took the drug up to 8 times a day. Thus, it was difficult to control or estimate food intake. Based on the results from Study JPC 3,4-DAP.PK1, C_{max} of 3,4-DAP was decreased but AUC remained similar under fed compared to fasted state. The sponsor

thought there was no impact of food intake on clinical response. The Division mentioned that, based on this PK study, as the sponsor recognized, administration of the drug with food mitigated some adverse events including abdominal discomfort.

Question e:

3,4-Diaminopyridine phosphate (amifampridine phosphate) has been designated as a Breakthrough Therapy for Lambert-Eaton Myasthenic Syndrome (LEMS). Can we assume that our NDA for 3,4-Diaminopyridine, which is the same active moiety, will be reviewed as a Rolling Review?

FDA Preliminary Response to Question e:

A request for rolling submission and review of portions of a marketing application only applies to products with Fast Track or Breakthrough Therapy designations. Your drug does not have either of these designations.

You would need to submit a request for Fast Track or Breakthrough therapy designation for your drug development program in order to be considered for the designation.

For further information regarding Fast Track designation, Breakthrough Therapy designation and the processes for Rolling Review, refer to the FDA *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

Meeting Discussion:

The Division stated that the sponsor should submit a Fast track designation request and that, on face, criteria are met to grant a Fast Track designation. Also, a CMC meeting should be scheduled quickly.

3.0 ADDITIONAL COMMENTS

Chemistry, Manufacturing and Controls (CMC)

We note that you have designated [REDACTED] ^{(b) (4)} as the starting material for the amifampridine drug substance. According to ICH Q11, you should select a starting material so that “enough of the drug substance manufacturing process is described in the application for regulatory authorities to understand how impurities are formed in the process; how changes in the process could affect the formation, fate, and purge of impurities; and why the proposed control strategy is suitable for the drug substance manufacturing process. This will typically include a description of multiple chemical transformation steps. [REDACTED] ^{(b) (4)}

starting material and the drug substance". [REDACTED] (b) (4)
[REDACTED] as the regulatory starting material. You should demonstrate that changes in the manufacturing process of starting materials will not affect the impurity profile and physical chemical properties of the drug substance.

You should include limits for particle size distribution in the drug substance specification. Alternatively, provide justification that a particle size test is not needed in the specification.

Meeting Discussion: No Meeting discussion.

Post-Meeting Note:

As mentioned in the June 17, 2014 meeting, we recommend that you request a CMC-only meeting to discuss the proposed content of the CMC related Modules of the application. The timing of the CMC submission may be discussed at that time.

Clinical Pharmacology

1. In the last submission (pre-NDA meeting package), you mentioned that a single-dose PK study in 10 volunteers was proposed. Please clarify the status of this study.
2. There appears to be no hepatic impairment study under design. If this is the case, please provide justification why you consider that a hepatic impairment study is not needed, and provide the proposed labeling language about dosing recommendation for patients with hepatic impairment.
3. You need to investigate the inhibition potential of 3,4-DAP and N-acetylated-3,4-DAP on NAT2 enzyme, if NAT2 is identified as the major enzyme for 3,4-DAP metabolism. Similarly, you would need to determine the protein binding of 3,4-DAP and possibly also N-acetylated-3,4-DAP in human plasma. Such information can be provided post- approval.

Meeting Discussion: No Meeting discussion.

3.1 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

3.2 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

3.3 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#)

(<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

3.4 PROSPECTIVE SUICIDALITY ASSESSMENTS IN CLINICAL PROTOCOLS

Treatment-emergent suicidality (suicidal ideation and behavior) has been identified in recent years as a concern for a number of drugs and drug classes. FDA-conducted meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drug classes increase the risk of suicidal thoughts and behavior. Spontaneous reports have led to concerns about the risk for suicidality with other drugs as well. These drugs include isotretinoin and other tretinoin, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss.

Given the heightened concern regarding the potential for treatment-emergent suicidality with certain drugs, particularly those products with central nervous system activity, the Division of Neurology (DNP) has made the determination that prospective assessments for suicidality should be included in clinical trials involving all drugs for neurological indications. There are two primary reasons for this new requirement pertaining to prospective suicidality assessments. First, such prospective assessments will ensure the collection of more timely, complete, and reliable data pertaining to suicidality than have been collected in the past. This will allow assessment of the risk for suicidality with a given drug and, when the data are collected in a systematic and uniform fashion, will allow for additional analyses to be conducted in the future aggregating findings and comparing findings across drugs and drug classes. Second, such prospective assessments will help ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed. This is important whether or not a particular product is known or suspected to be associated with treatment-emergent suicidality.

All clinical protocols for products developed in DNP for any indication should therefore include a prospective assessment for suicidality. These assessments must 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. It is reasonable to omit such assessments from these trials. An acceptable instrument should map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), directly classifying events of interest into one of 11 categories of suicidal ideation and behavior. The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument.

You must obtain DNP's prior approval for any alternative assessment instrument that you wish to use. A request to use an alternative prospective suicidality assessment instrument should include a justification for the use of this instrument, including an explanation of how the alternative instrument would map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). As discussed above, the ability of an assessment instrument to map to a common scale is important for any analyses conducted in the future.

This new policy is applicable to all new protocols submitted to DNP and to ongoing protocols in which you have an IND residing within DNP. For ongoing protocols, amendments must be submitted to incorporate this assessment. For newly submitted protocols drafted prior to you becoming aware of this new policy, the lack of a prospective assessment for suicidality will not constitute a reason for placing your IND on clinical hold. As with ongoing protocols, an amendment should be submitted to incorporate such assessments. In the future, however, the absence of a plan for prospective suicidality assessments may constitute a reason for placing an IND on clinical hold.

It is reasonable to omit prospective assessments for suicidality, or consider alternative assessments, in trials involving patients with impairment that is so substantial as to interfere with such assessment.

A sponsor considering the omission or alteration of standard suicidality assessments from a particular clinical protocol should discuss this omission with DNP to gain prior agreement. In certain instances, alternative instruments may permit the assessment of suicidality.

Further details pertaining to the prospective assessment of the occurrence of suicidality in clinical trials can be found in the following Draft Guidance for Industry:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Post-meeting electronic communication on June 27, 2014: sponsor's proposed timelines for submission of portions of an NDA application.

Approximate Time Lines

Chemistry, Manufacturing and Controls Section		Estimated Submission 4Q 2014
Non-Clinical Pharmacology and Toxicology Section		Estimated Submission 4Q 2015
Outstanding Individual Components	Initiation Date	Estimated Completion Date
6-Month Chronic Toxicology Study (rat) + 10 week analysis	Sept 2014	May 2015
Dose Finding Studies (dog)	Aug 2014	Oct 2014
9-Month Toxicology Study (dog) + 10 week analysis	Nov 2104	Oct 2015
In vitro Safety Screen	July 2014	Aug 2014
NAT2 Substrate determination	July 2014	Aug 2014
Effects of 3,4-DAP and 3-Ac metabolite at the Murine Neuromuscular Junction	On-going	Nov 2014
Human Pharmacokinetics and Bioavailability Section		Estimated Submission 4Q 2014
Individual Components	Initiation Date	Estimated Completion Date
Urine Excretion (JPC 3,4-DAP.PK1 study in normal volunteers)	On-going	Aug/Sept 2014
PK/PD in LEMS (3,4-DAP and 3-Ac metabolite)		Sept/Oct 2014
Clinical Data Section		Estimated Submission 4Q 2014
Individual Components	Initiation Date	Estimated Completion Date
Clinical Trial Data Back-up submitted to the FDA (supporting data, paper CRFs)	On-going	July 2014
Renal Insufficiency Study: DAPPER & Compassionate Use		Sept/Oct 2014
Long Term Safety Study 52 DAPPER Screenees (Protocol and SAP finalized, will be submitted by July 2014)	July 2014	Sept/Oct 2014
Assessment of the effect of 3,4-DAP on cardiac intervals in LEMS patients on long-term 3,4-DAP treatment participating in the DAPPER trial	On-going	Sept/Oct 2014

Approximate Time Lines

Statistical Section		Estimated Submission 4Q 2014
Individual Components	Initiation Date	Estimated Completion Date
PK/PD in LEMS (3,4-DAP and 3-Ac metabolite)		Sept/Oct 2014
Expanded Statistical Analysis Plan (SAP) DAPPER		July 2014
Statistical Data (Data Lock)		Aug 2014
Statistical Data (Final Report)		Oct 2014

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

/s/

ERIC P BASTINGS
07/17/2014



IND 54,313

MEETING MINUTES

Jacobus Pharmaceutical Company, Inc.
Attention: David P. Jacobus, M.D.
37 Cleveland Lane
P.O. Box 5290
Princeton, NJ 08540

Dear Dr. Jacobus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 3,4-diaminopyridine.

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2010.

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

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

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

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 7, 2010; 12:00 – 1:00 PM EST
Meeting Location: CDER WO Room 1309

Application Number: IND 54,313
Product Name: 3,4-diaminopyridine
Indication: Lambert-Eaton Myasthenic Syndrome (LEMS),
(b) (4)

Sponsor/Applicant Name: Jacobus Pharmaceuticals Company, Inc.

Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Stephanie N. Keefe

FDA ATTENDEES

Russell G. Katz, M.D., Division Director, DNP
Ron Farkas, M.D., Clinical Team Leader, DNP
Andrew Sostek, Ph.D., Clinical Reviewer, DNP
Martha Heimann, Ph.D., CMC Lead, DNP
Lois Freed, Ph.D., Non-Clinical Supervisor, DNP
Richard Houghtling, Ph.D., Non-Clinical Reviewer, DNP
Angela Men, Ph.D., Clinical Pharmacology Team Leader, DNP
Xinning Yang, Ph.D., Clinical Pharmacology Reviewer, DNP
Jingyu Luan, Ph.D., Biometrics Reviewer, DNP
Charlene Flowers, Safety Reviewer, OSE
Stephanie N. Keefe, Regulatory Project Manager, DNP

SPONSOR ATTENDEES

David R. Jacobus, M.D.
Guy A. Schiesher, M.D.
Kathy L. Ales, M.D.
Laura Jacobus
Donald B. Sanders, M.D.
Constance M. Bowe, M.D.

1.0 BACKGROUND

Jacobus Pharmaceutical Company, Inc. received Orphan Designation for the use of 3,4-DAP for the LEMS indication in December 1990. It is estimated that the number of patients is 1 per 100,000 population [REDACTED] (b) (4)

[REDACTED] Jacobus has supported physician-held IND's since mid-1993.

Jacobus is requesting a preNDA meeting to expand the studies to all those needed for registration. The proposal is to present three placebo-controlled prospective clinical studies using their material [REDACTED] (b) (4) and provide a summary of current and prior 3,4-DAP usage under investigator sponsored IND's.

2. QUESTIONS

I. [Questions submitted in the August 10, 2010 Briefing Document]

QUESTION 1: We consider that the four clinical trials along with the confirming data (Jacobus cohort) establish that 3,4-DAP is safe and effective for the proposed claims. Do you think that there is a reasonable chance that the clinical data is acceptable?

FDA Preliminary Response

No. The efficacy studies that you present in LEMS are all of very short duration; for example, the placebo-control period is only 6 days in the Duke study, while in the McEvoy study 8 days of dose escalation is followed by 3 days of crossover treatment. Because 3, 4 DAP would be a chronic therapy used for months or years, the division would require a new placebo-controlled study showing sustained efficacy in LEMS for at least 3 months.

Potentially a randomized withdrawal design for such a study would be appropriate, to minimize the length of placebo treatment, although other designs would be advantageous for documenting safety. A randomized withdrawal design could enroll mainly currently-treated patients, although new patients could also be enrolled so long as they were treated for 3 months before the randomized withdrawal phase. The efficacy endpoint for the 3 month study should reflect important patient function(s).

Potentially the short-duration studies you cite could be used in combination with the new study to provide independent substantiation of efficacy, but importantly, these studies would be of greatest support only if the complete protocols, statistical analysis plans, and source data (including, for example, case report tabulations and case reports forms, as described in CFR 21, 314.50) were submitted in adequate detail to allow re-analysis and confirmation of study findings.

(b) (4)

(b) (4)

Meeting Discussion

The sponsor indicated they plan to conduct an additional phase 3 study to show sustained efficacy, a thorough QT study, and clinical pharmacology and non-clinical studies. The sponsor also indicated that they will be able to submit the original data from the efficacy trials they cited.

The sponsor then gave an overview of LEMS

(b) (4)

The sponsor asserted that LEMS patients did not spontaneously improve or remit, but rather tended to reach a plateau of clinical symptoms. The sponsor additionally noted that periodic washout had been done in some LEMS patients, and that clinical worsening on washout had indicated that the drug was still effective. Moreover, the sponsor noted that 3,4-DAP might have a cumulative effect, and therefore might be more effective after many months of treatment or longer.

(b) (4)

The discussion then turned to design of the trial to show sustained efficacy over 3 months. The sponsor passed out an outline of a study that involved several study periods. The division stated that a study with fewer periods would be acceptable, such as a 3-month parallel arm placebo-controlled study, or a randomized-withdrawal study in which patients on drug for 3 or more months would be randomized to drug or placebo, with an endpoint based on a clinically meaningful measure of 'failure'. It was discussed that since patients would all have been on drug, bias might be introduced from patient's ability to discern the switch to placebo. Also, the division expressed concern that sudden switch to placebo could cause a withdrawal phenomenon wherein patient condition would worsen compared to what would otherwise have been baseline, although the sponsor indicated that in their experience with withdrawing drug, such withdrawal phenomenon did not occur. The division raised the possibility that these potential confounders could be addressed through appropriate study design, and noted, for example, that slow titration from open-label drug treatment to randomized drug or placebo treatment might decrease the risk of withdrawal effects, and might also decrease patient perception of being switched from drug to placebo. The division stated that other study designs might also be acceptable. While the sponsor noted that it would be possible to compare patients after drug withdrawal to their baseline up to many years earlier, the division stated that this didn't seem necessary to address the concern about

withdrawal effects, and in any case, it was not clear that the disease would be adequately stable over many years to make such a comparison meaningful.

The sponsor asked about patient enrolment criteria, and the acceptability of excluding subsets of LEMS patients, such as those with particularly mild or severe disease. The division responded that such criteria were typical of registration trials, and could be acceptable, although it would be a matter for review of the protocol.



Discussion then turned to efficacy endpoints. Improvement in walking, shown both objectively and subjectively, would be acceptable to the division, although other measures of function would also be acceptable. The division stated that the ‘muscle strength’ measurement was problematic because, particularly in the case of a small drug effect, a positive test of muscle strength might not actually translate into clinically meaningful benefit. Similarly, the QMG score was problematic because some measures, for example ptosis, were measured using maneuvers that would not be encountered in normal activity (i.e. upward gaze for more than 1 minute), such that extrapolation was necessary to conclude change in the patients ordinary daily activity. However, the sponsor pointed out that they had employed a “modified” QMG which might allay the division’s concerns. It was agreed that electrophysiological endpoints would be useful objective supporting evidence that would be less susceptible to certain forms of bias.



The necessary size of efficacy studies was then discussed. The division stated that there was no requirement that placebo-controlled trials needed to be larger than necessary to establish efficacy.

The discussion then turned to the necessary safety database. While the sponsor had experience with a large number of patients treated over a number of years, the division stressed that the sponsor would have to show that safety data from these patients had

been collected adequately to support an NDA - essentially to the standards of a prospective long-term safety study.

It was agreed that the sponsor should submit their protocol for review, and that the division will give detailed feedback, including on the primary endpoint.

QUESTION 2: We have attached a list of supporting studies necessary to determine safety and support the management of the drug. We hope that every test required by the FDA as a prerequisite to marketing is on this list. Supporting tests can be important; we welcome suggestions. However, we are not certain if some of the preclinical tests suggested for compounds which have not been in man are still appropriate in the absence of clinical complications.

FDA Preliminary Response

It is not clear from your submission if safety data (both from short- and long-term exposures) was collected with adequate detail and quality-control to be acceptable. If not, it may still be possible to gather such data at this point, but only if detailed and reliable clinical notes were recorded in patient charts at the actual time events occurred.

As stated under question 1 regarding efficacy data, safety data from the short-term controlled trials you cite should be submitted in detail, including the complete protocols, case report tabulations and case report forms.

We have the following comments on your nonclinical plan described in the briefing package:

- *You have proposed conducting more than the standard battery of genotoxicity studies (cf. Guidance for Industry S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals” July 1997). Typically, the standard battery is sufficient, unless the results of these studies indicate that additional studies are needed (cf. Guidance for Industry and Review Staff: Recommended Approaches to Integration of Genetic Toxicology Study Results” January 2006).*
- *To assess the carcinogenic potential of 3,4-DAP, you propose to conduct only a 6-month p53^{+/-} transgenic mouse study. The appropriateness of this assay cannot be determined in the absence of data from the genotoxicity studies. We would recommend that you consider the TgrasH2 transgenic model, which is sensitive to both genotoxic and non-genotoxic compounds. In addition, you will need to conduct a 2-year carcinogenicity study in rat.*
- *Your plan for assessing reproductive and developmental toxicity is unclear. We refer you to the following guidance for information on the recommended battery of studies: Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility S5(R2) ICH Nov 2005.*

- *We agree that no additional immunotoxicology studies will be needed if there is no evidence of immunosuppression or immunotoxicity with repeated administration of 3,4-DAP.*
- *You will need to demonstrate that major circulating metabolites in humans (if any) are adequately assessed in nonclinical studies.*
- *If you intend to develop 3,4-DAP for treatment of pediatric patients, you will need to conduct a juvenile animal toxicology study in one species. We would recommend that you submit a final study protocol for our comment prior to study initiation.*

Considering the intended patient population(s), it is possible that some portions of the nonclinical program may be submitted post-approval. It would be expected, however, that the genotoxicity studies will be completed as soon as possible and that the planned chronic toxicity studies in rodent and non-rodent will be completed prior to NDA submission. The timing of submission of the chronic studies in relationship to the conduct of clinical trials will depend on the nature of the clinical trial(s) proposed and the extent of previous human experience.

Meeting Discussion

The Sponsor intends to submit a new IND for 3,4-DAP for treatment of Lambert Eaton Myasthenic Syndrome and requested clarification on the need for nonclinical studies prior to initiation of a clinical trial in that population. The Division noted that no nonclinical data will be needed since the clinical trial is to be conducted in patients currently being treated with 3,4-DAP.

QUESTION 3: Neurological medications often have a limit in their total dosage which precludes the administration of enough of the drug to produce systemic tissue lesions. We have provided a list of studies which we believe are essential in order to ensure safety and are open to the suggestion that additional studies should be added. We would like you to review this list and add suggestions.

FDA Preliminary Response

See Preliminary Response to Question 2.

Additional Comment (CMC)

Your proposed

(b) (4)

Therefore, you will need to control this impurity at a level consistent with its potential toxicity. Alternatively, you may qualify this impurity in an appropriate battery of nonclinical genotoxicity assays. Additionally,

we recommend that you evaluate (b) (4) obtained commercially for the presence of this impurity or other potentially genotoxic impurities.

Additional Comments (Clinical Pharmacology)

1. Your proposed labeling states that 3,4-DAP is largely cleared unchanged in the urine. However, the evidence provided in your submission actually refers to an analog of 3,4-DAP, 4-aminopyridine. You plan to collect blood and urine samples in the proposed PK and TQT study. You need to analyze the concentrations of 3,4-DAP in these samples to provide evidence for the claim that 3,4-DAP is mainly cleared unchanged through urine. In addition, you should consider conducting a mass-balance study.

2. In your proposed labeling, 3,4-DAP will be administered with or without food. However, in the proposed PK and TQT study, 3,4-DAP will be administered with food in order to reduce side effects such as abdominal discomfort. A food effect study needs to be conducted to determine the impact of food on the PK of 3,4-DAP.

(b) (4)

4. In the section of pre-clinical and toxicology tests, you listed in vitro metabolism, inhibition and induction potential, and P-glycoprotein transporter studies. However, you did not provide an outline for the P-glycoprotein transporter study. You need to investigate whether 3,4-DAP is a substrate or inhibitor of P-glycoprotein in vitro.

5. Based on results of renal clearance and/or mass-balance study, a renal impairment study needs to be considered.

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
10/11/2010