CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205579Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205579 SUPPL # 000 HFD # 170

Trade Name Ryanodex

Generic Name dantrolene sodium

Applicant Name Eagle Pharmaceuticals, Inc.

Approval Date, If Known July 22, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

A safety, tolerability, and PK study was conducted to determine whether Ryanodex was bioequivalent to Dantrium IV (the referenced product) and to determine whether there were any safety issues unique to Ryanodex due to the greater exposure it provides to dantrolene sodium.

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d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 018264 Dantrium IV

NDA# 017443 Dantrium Capsule

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

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Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND #105411 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

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(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Mavis Darkwah, PharmD
Title: Regulatory Project Manager
Date:

Name of Office/Division Director signing form:
Title:

Reference ID: 3597644

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Reference ID: 3597644

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

/s/

MAVIS Y DARKWAH
07/22/2014

RIGOBERTO A ROCA
07/22/2014

1.3.3 DEBARMENT CERTIFICATION

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. Section 335a(k), Eagle Pharmaceuticals, Inc.("Eagle") hereby certifies that Eagle did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

David Rohrbach July 10, 2013

David Rohrbach Date:

Vice President, Quality and Compliance

9th July 2013.

Paul Bruinenberg, MBChB, MBA Date:

Chief Medical Officer

Reference ID: 3602867

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205579 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Ryanodex Established/Proper Name: dantrolene sodium Dosage Form: lyophilized powder for injectable suspension 250mg/vial		Applicant: Eagle Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Mavis Darkwah, PharmD		Division: Division of Anesthesia, Analgesia, and Addiction Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 06/30/2014

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is July 22, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

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Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 07/22/2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable letter 02/12/2014 Reviews 02/10/2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None DMEPA: 07/09/2014, 07/17/2014 ☐ None DMPP/PLT (DRISK): ☒ None OPDP: 06/30/2014 ☒ None SEALD: ☐ None CSS: ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	RPM Filing Review 03/26/2014 ☐ Not a (b)(2) 06/23/2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

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• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Drug has Orphan Drug designation	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Several
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg August 7, 2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg January 26, 2011
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 07/22/2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 07/14/2014
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	07/02/2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	07/11/2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Maternal Health05/21/2014 and 07/15/2014 Division of Pharmacovigilance II,

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	07/18/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 06/19/2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 07/14/2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 06/27/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 06/27/2014
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 06/27/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 07/01/2014 and 07/11/2014 ONDQA Biopharmaceutics review: 06/24/2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 06/19/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	07/01/2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☒ Acceptable 04/14/2014 ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3598924

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

/s/

MAVIS Y DARKWAH
07/24/2014

From:	Foma Rashkovsky
To:	Darkwah, Mavis
Cc:	Foma Rashkovsky
Subject:	RE: NDA 205579 Label Information Request
Date:	Monday, July 21, 2014 9:37:36 AM
Attachments:	NDA 205579 Prescribing Information 07-21-14 [all FDA changes accepted].doc

Dear Mavis,

Attached please find the final revision of the Ryanodex Prescribing Information.
When we should expect the approval letter?

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Friday, July 18, 2014 5:07 PM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Label Information Request
Importance: High

Dear Foma,

We have accepted your proposed changes we agree with, and rejected the proposed changes we do not agree with. We have also added information to the labeling. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide clean copy of the word version.

Please respond with revised labels ASAP, preferably, by 11AM July 21, 2014.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Thursday, July 17, 2014 1:00 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Label Information Request

Dear Mavis,

Attached are two Word files of revised Prescribing Information: one as a clean copy and the other one in tracked-changes.
I hope that we satisfied all your requirements.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]

Sent: Wednesday, July 16, 2014 12:52 PM
To: Foma Rashkovsky
Subject: NDA 205579 Label Information Request
Importance: High

Dear Foma,

Please refer to your NDA 205579. Attached please find the word version of the label with our proposed changes. We have accepted your proposed changes we agree with, and rejected the proposed changes we do not agree with. We have also added information to the labeling. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide clean copies of the word version.

Please respond with revised labels ASAP, preferably, by 12PM July 18, 2014.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately f ll i thi

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

/s/

MAVIS Y DARKWAH
07/24/2014

From: Foma Rashkovsky
To: Darkwah, Mavis
Subject: RE: NDA 205579 Labeling information request
Date: Friday, July 18, 2014 5:55:27 PM

Mavis,

Thank you for the both emails. Have a great weekend.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Friday, July 18, 2014 5:08 PM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Labeling information request
Importance: High

Foma, Please submit the final approved vial and carton label officially to the NDA.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Thursday, July 17, 2014 3:35 PM
To: Darkwah, Mavis
Subject: RE: NDA 205579 Labeling information request

Thank you so much. Have a nice day.

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Thursday, July 17, 2014 3:33 PM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Labeling information request

Dear Foma,

The revised vial and carton labels are acceptable, and we have no additional comments.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Thursday, July 17, 2014 12:15 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky

Subject: RE: NDA 205579 Labeling information request

Dear Mavis,

Attached please find revised vial and carton labels as directed in your email below.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, July 16, 2014 11:10 AM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Labeling information request

Dear Foma,

Please review the request below concerning the revised carton and container label you submitted on July 14, 2014:

Carton Labeling and Container Labels

1. The new graphic placed in close proximity to the proprietary name, established name, and strength can distract a reader from this critical information. Remove the graphic or place it elsewhere on the principal display panel so that it does not distract the reader from this critical information.

2. Include the Lot Number and Expiration Date on the vial label.

Please respond with revised labels ASAP, preferably, by 4PM July 17, 2014.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Monday, July 14, 2014 4:57 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Labeling information request

Dear Mavis,

Attached are revised container and carton labels. The following is summary of changes:

A. General Comments for All Labels and Labeling
Replaced “For treatment of malignant hyperthermia” text with "For [redacted] (b) (4) of malignant hyperthermia, along with the appropriate supportive measures"

- Please note that word “treatment” was replaced with word “ (b) (4) ” to comply with wording in the current Prescribing Information.

B. Container Label and Carton Labeling

1. Revised the established name to be at least ½ the size of the proprietary name

2. Revised the strength statement from “250 mg/vial” to read “250 mg per vial”.

    - Decreased the size of the strength statement (orange area and text)

3. "Reconstitution yields 50 mg/mL" was directly placed below the strength statement which now reads "250 mg per vial"

-

4. Revised the statement “ (b) (4) ” on the principal display panel to read “Reconstitute with Sterile Water for Injection, USP” to fit on one line.

5. Added parenthesis to the established name dantrolene sodium so that the product name reads Ryanodex® (dantrolene sodium) for injectable suspension.

6. The text “Each single-use vial contains… to yield a pH of approximately (b) (4) …” has been revised to “Each single-use vial contains… to yield **a suspension with** a pH of approximately **10.3** …”.

7. The text “Store unreconstituted product at (b) (4) and avoid prolonged exposure to light.” has been revised to “Store unreconstituted product at 20 °C to 25 °C (68 ºF to 77 ºF) [see USP Controlled Room Temperature] and avoid prolonged exposure to light.”

8. Added the following new text to the side pane to read “Use within 6 hours after reconstitution. Store reconstituted suspension at controlled room temperature 20 °C to 25 °C (68 ºF to 77 ºF). Protect from light.”

9. Replaced the statement “ (b) (4) ” with “Single Use Only – Discard Unused Portion”

    - Please note that “ (b) (4) ” was replaced with “Single Use Only – Discard Unused Portion” on the Container Labeling to be consistent with the Carton Labeling.

C. Carton Labeling

1. Replaced the statement “ (b) (4) ” with “Single Use Only – Discard Unused Portion”
2. Eagle Pharmaceuticals, Inc.’s company logo was added to the side panel with the barcode.
3. Part Number PC4772 was added to the side panel flap.

We trust this meets with your requirements.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Thursday, July 10, 2014 3:33 PM
To: Foma Rashkovsky
Subject: NDA 205579 Labeling information request
Importance: High

Dear Foma,

Please refer to your NDA 205579. Below are the comments and recommendations for the container label and carton labeling. Please send revised container and carton labeling incorporating the requested changes. Please indicate in your response any recommendation you do not agree with and your rationale for your decision. The PI labeling request will be sent later in a different correspondence.

A. General Comments for All Labels and Labeling

We note that a partial indication, "For treatment of malignant hyperthermia", is present on the proposed carton and the vial labeling. We recommend that the full indication (including the "along with appropriate supportive measures") is presented.

B. Container Label and Carton Labeling

1. Revise the established name to be at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2). Ensure that the proprietary and established names are the most prominent information on the label and labeling.

2. Revise the strength statement from "250 mg/vial" to read "250 mg per vial".

3. Add the amount of drug contained in each milliliter once reconstituted to the principal display panel (PDP) to include this important information to assist with dosing. The language can read similar to "After reconstitution, each vial contains 50 mg/mL" and should be placed under the statement of strength. Consider moving the indication for use statement to the side panel to accommodate this information.

4. Revise the statement "[redacted] (b) (4)" on the principal display panel to read "Reconstitute with Sterile Water for Injection, USP" and ensure it appears on one line.

5. Add parenthesis to the established name dantrolene sodium so that the product name reads Ryanodex (dantrolene sodium) for injectable suspension.

6. The text "Each single-use vial contains… to yield a pH of approximately [redacted] (b) (4) …" should be

revised to "Each single-use vial contains… to yield **a suspension with** a pH of approximately **10.3** …".

7. The text "Store unreconstituted product at [redacted] (b) (4) and avoid prolonged exposure to light." should be revised to "Store unreconstituted product at 20 °C to 25 °C (68 ºF to 77 ºF) [see USP Controlled Room Temperature] and avoid prolonged exposure to light."

8. Add a new text to read "Use within 6 hours after reconstitution. Store reconstituted suspension at controlled room temperature 20 °C to 25 °C (68 ºF to 77 ºF). Protect from light."

C. Carton Labeling

1. Replace the statement [redacted] (b) (4) with "Single Use Only – Discard Unused Portion".

We request a response as soon as possible, preferably by close of business July 14, 2014.

Let me know if there are any questions.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MAVIS Y DARKWAH
07/21/2014

From: Foma Rashkovsky
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Label Information Request
Date: Thursday, June 26, 2014 2:30:03 PM
Attachments: revised-section-12-3.docx

Dear Mavis,

Attached is revised section **12.3 Pharmacokinetics** of our Prescribing Information for Ryanodex. Let me know if you need an official submission of this section.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Tuesday, June 24, 2014 2:48 PM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Label Information Request

Dear Foma,

Thank you for the response and concurrence to include the proposed changes in the label. Please submit section 12.3 incorporating the requested information below and attached document:

Note to sponsor: Describe ONLY dantrolene PK following 2.5 mg/kg of **Ryanodex** administration. Describe the specific method of administration of Ryanodex employed (bolus into line etc.) in the PK study in healthy volunteers. Generally, provide a table of critical PK measures, such as maximum concentration (Cmax), AUC, half-life (t1/2), clearance (CL), and volume of distribution (Vd). Indicate that the time to maximum concentration (Tmax) appeared to be in the first sample of blood collected.
Describe pertinent pK parameters of the measured metabolite 5-hydroxy dantrolene.

Please respond via email as soon as possible, no later than 3PM (eastern), June 26, 2014.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Tuesday, June 24, 2014 1:48 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Label Information Request

Dear Mavis,

In response to your email below Eagle is in concurrence to incorporate these changes in the label.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, June 23, 2014 12:57 PM
To: Foma Rashkovsky
Subject: NDA 205579 Label Information Request
Importance: High

Dear Foma,

Please refer to your NDA 205579 and the label that was submitted. Modify the 12.3 Pharmacokinetics section of the NDA 205579 (Ryanodex) label with the attached instructions provided. Please respond via email as soon as possible, no later than COB, July 25, 2014, with your concurrence to incorporate these changes in the label during the labeling negotiation (in a few weeks). There is no need to send a revised label at this time.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Label (vial &carton) Information Request
Date: Tuesday, July 01, 2014 10:35:00 AM
Importance: High

Dear Foma,

Please refer to your NDA 205579 and the labeling that was submitted. Please modify the vial and carton label with the request below:

1. Add parenthesis to the established name dantrolene sodium so that the product name reads Ryanodex (dantrolene sodium) for injectable suspension.

2. The text "Each single-use vial contains… to yield a pH of approximately (b) (4) …" should be revised to "Each single-use vial contains… to yield **a suspension with** a pH of approximately **10.3** …".

3. The text "Store unreconstituted product at (b) (4) and avoid prolonged exposure to light." should be revised to "Store unreconstituted product at 20 °C to 25 °C (68 ºF to 77 ºF) [see USP Controlled Room Temperature] and avoid prolonged exposure to light."

4. Add a new text to read "Use within 6 hours after reconstitution. Store reconstituted suspension at controlled room temperature 20 °C to 25 °C (68 ºF to 77 ºF). Protect from light."

Please respond via email as soon as possible, no later than 12PM (eastern), July 7, 2014, with your concurrence to incorporate these changes in the labeling during the labeling negotiation (in a few weeks). There is no need to send a revised vial and container label at this time.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
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/s/

MAVIS Y DARKWAH
07/02/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Monday, June 23, 2014 2:34:00 PM
Importance: High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request:

In reference to the pivotal GLP study entitled *Evaluation of the efficacy and safety of Dantrolene in the treatment of malignant hyperthermia in susceptible swine* (Study report #1773-004), the mean Cmax value for the Dantrium IV 2.5 mg/kg group (18,181 ng/mL) appeared aberrantly high as it was approximately 3-fold and 1.5-fold higher than the Cmax values from the Ryanodex 2.5 mg/kg group (6,860 ng/mL) and the Dantrium 10 mg/kg group (12,781 ng/mL). The study report included a protocol deviation that noted that "the proximal lumen of the central line was used to administer the comparator article (2.5 mg/kg Dantrium IV) to animal number 413, rather than the protocol-specified distal lumen" and that the 1 minute sample was collected while the Dantrium IV was still being administered. We acknowledge that this may have been attributable for the aberrantly high dantrolene concentration (38,400 ng/mL) that was observed in this animal at the 1 minute time point. However, dantrolene concentrations appeared aberrantly high at the 1 minute time point for several animals (e.g., 419, 441, 402, 424, 438) from the Dantrium IV 2.5 mg/kg group. Provide an explanation for the aberrantly high dantrolene concentrations at the 1 minute time point for these animals from the Dantrium IV 2.5 mg/kg group.

Provide response, via email, as soon as possible, no later than 4PM, June 25, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
06/23/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Tuesday, June 17, 2014 12:15:00 PM
Importance: High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request:

1. **Your proposed labeling states that [redacted] (b) (4) [redacted] Provide compatibility data to support the use of your product with these solutions.**

2. **Section 2.5 of your proposed labeling states that "… [redacted] (b) (4) [redacted] to ensure an orange colored uniform suspension." However, your reconstitution studies were conducted using [redacted] (b) (4) samples. Provide data to demonstrate that the lyophilized product can be reconstituted with [redacted] (b) (4) to produce the desired nanosuspension for injection and any settled drug within the six hour in-use period can be re-suspended with [redacted] (b) (4) [redacted] as well.**

3. **Provide data on the photostability of the reconstituted suspension.**

4. **Include an in-process control for drug particle size distribution in the [redacted] (b) (4) step of the drug product manufacturing process.**

Provide responses, via email, as soon as possible, no later than 3PM June 23, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
06/17/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Wednesday, June 04, 2014 7:41:00 AM
Importance: High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

We note that the minipig efficacy and toxicology studies were conducted at (b) (4), which appears to be the same site that the clinical samples with suspected hemolysis were stored. Is there any visual evidence of suspected hemolysis in the nonclinical blood samples from the pivotal GLP minipig efficacy and toxicology studies?

Please provide responses, via email, as soon as possible, no later than COB June 6, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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MAVIS Y DARKWAH
06/04/2014

From:	Darkwah, Mavis
To:	frashkovsky@eagleus.com
Subject:	NDA 205579 Information Request
Date:	Tuesday, May 27, 2014 2:45:00 PM
Importance:	High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

From the Part 2 of the clinical study evaluating PK of 2.5 mg/kg dose of Ryanodex and Dantrium provide the following:

1. **Indicate the status of each and every single plasma sample with regard to the color of sample (indicate if the sample is red, orange, yellow), also indicate whether the stored samples used for calibration curve have the color.**
2. **Comment on the status of the sample with regard to hemolysis (Hemolysis status – Yes or No)**
3. **Indicate the color of the plasma sample isolated from blood that is spiked with Ryanodex at concentrations similar to the noted peak plasma concentration, (e.g. whether the samples at Cmax has a deeper color compared to samples with lower drug concentration.)**

For items 1-3, a table [sample (time relative to dosing) by subject number] accounting for all samples would be helpful way to organize your response to these requests.

4. **Indicate the impact of hemolysis, even suspected, on the plasma concentration. With regard to this, indicate the blood to plasma partitioning of dantrolene following Ryanodex administration. Please submit any study you have done to address this issue.**

Please provide responses, via email, as soon as possible, preferably by COB June 2, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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MAVIS Y DARKWAH
05/28/2014

From:	Darkwah, Mavis
To:	frashkovsky@eagleus.com
Subject:	NDA 205579 Information Request
Date:	Wednesday, May 28, 2014 8:04:00 AM
Importance:	High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

As requested before, revise the definition of Q in the dissolution acceptance criterion. This request is based on the fact that the Q* cannot differentiate two batches with different release profiles, for example, the two batches with different particle sizes as shown in Table 11 and Table 12 on page 9 of your dissolution method development report (rpt36604-00-tp66457-v2.pdf).

Please provide responses, via email, as soon as possible, no later than COB June 2, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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MAVIS Y DARKWAH
05/28/2014

From:	Darkwah, Mavis
To:	frashkovsky@eagleus.com
Subject:	NDA 205579 Information Request
Date:	Tuesday, May 27, 2014 2:54:00 PM
Importance:	High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

-

Analyze and provide a summary report with individual subject listings on the hemoglobin concentration for each of the PK specimens for Study 1201.

Please provide responses, via email, as soon as possible, preferably by COB June 6, 2014, and follow with an official submission to the NDA. Inform us as soon as possible if this request will not be feasible or if it will take longer.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
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MAVIS Y DARKWAH
05/28/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Friday, May 23, 2014 3:36:00 PM

Dear Foma,

Please refer to your NDA 205579 and respond to the request below:

Please send us the following:

5 vials of the to-be-marketed formulation of Ryanodex
5 vials of sterile water for injection (the same as used in the clinical studies) and syringes

5 vials of Dantrium IV
5 vials of sterile water for injection (the same as used in the clinical studies) and syringes

Please send the requested items as soon as possible, preferably, not to arrive no later than end of next week, May 30, 2014. Please address the requested items to my attention:

Mavis Darkwah, Pharm.D.
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 3111
10903 New Hampshire Avenue
Silver Spring, MD 20993
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/27/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Friday, May 16, 2014 2:45:31 PM

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request:

-

The drug substance synthesis impurity (b) (4) was evaluated at FDA for genetic toxicity using (quantitative) structure-activity relationship [(Q)SAR] models and was predicted to be positive for *Salmonella* and *E. Coli* mutagenicity. The Agency's current stance on the acceptable daily intake of mutagenic impurities, which is outlined in the ICH M7 Draft Consensus Guideline *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, allows up to 120 mg/day for an individual mutagenic impurity in a drug with intended treatment duration of £ 1 month. Therefore, you must lower the drug substance specification limit to NMT (b) (4) % for (b) (4), which is based on the recommended maximum daily dose of 10 mg/kg of dantrolene sodium. Alternatively, you can demonstrate that (b) (4) is negative in an appropriately conducted GLP-compliant bacterial mutagenicity assay.
Refer to the ICH M7 draft guideline which can be located at the following website.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf

Please respond via email as soon as possible, preferably by COB May 23, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/16/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Bcc: Darkwah, Mavis
Subject: NDA 205579 Information Request
Date: Thursday, May 15, 2014 3:33:00 PM

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

[redacted] (b) (4)

Please respond via email as soon as possible, preferably by May 28, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/15/2014

From: Foma Rashkovsky
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579: Urgent Request
Date: Monday, May 05, 2014 4:53:19 PM

Dear Mavis,

The BE study EGL-Dantrolene-1201 documents are currently located at a storage facility at (b) (4) [redacted]. Please contact Dr. Ruckle (study PI) prior to visiting this facility. His contact information is as following:

Jon L. Ruckle, M.D.
(current affiliation: Pacific Pharma Group)
Telephone Nos.:
(b) (4) [redacted]

Please note that this information is also provided on the 2-nd page of our Attachment A of 356h form.

Let me know if you have any questions.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, May 05, 2014 3:58 PM
To: Foma Rashkovsky
Subject: NDA 205579: Urgent Request
Importance: High

Dear Foma,

The Agency was informed that Comprehensive Clinical Development (CCD), the clinical site for BE study EGL-Dantrolene-1201, went out of business in June of 2013. Please provide the location of the study records for the clinical portion of the BE study EGL-Dantrolene-1201.

Your immediate attention to this request is needed.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/06/2014

From: Foma Rashkovsky
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Information Request
Date: Monday, April 28, 2014 3:11:18 PM

Dear Mavis,

Our response is as follows:

We did not measure fibrinogen or reticulocyte count in our clinical study, and we have no samples remaining from which these values could be generated.

Please let me know if you have any additional inquiries regarding this request.

BTW, are there any feedback regarding IR for SAS transport files for study 1773-004?

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, April 28, 2014 8:07 AM
To: Foma Rashkovsky
Subject: NDA 205579 Information Request
Importance: High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

Were fibrinogen and reticulocyte counts assessed in any of the human subjects? If so provide the data. If not, are blood samples still available that can be used to make these assessments? If so, please make the assessments and submit the data.

Please respond via email as soon as possible if the data is available. If the data is not available and assessments need to be done, then preferably by Mid-May, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/05/2014

From:	Darkwah, Mavis
To:	frashkovsky@eagleus.com
Subject:	NDA 205579 Information Request
Date:	Tuesday, April 22, 2014 10:04:00 AM
Importance:	High

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

Provide the SAS transport file(s) for Study 1773-004 entitled "Evaluation of the efficacy and safety of dantrolene in the treatment of malignant hyperthermia in susceptible swine." If they have previously been submitted, provide the submission number, date, and location.

Please respond via email as soon as possible, no later than COB April 28, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/05/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Tuesday, April 29, 2014 3:19:00 PM

Dear Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request

Provide, or indicate where in the NDA submission one can find the following clinical information for the integrated safety database:

1. **The descriptions of the analyses performed on the safety data bases to evaluate the adverse events (e.g., dose-dependence, relationship to subject demographics), and laboratory, vital signs, and ECG parameters (e.g., central tendency, shifts from baseline, outlier analyses as well as dose-dependence).**

2. **Tables summarizing the findings (not the detailed listings)**

Please respond via email as soon as possible, preferably by May 2, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
05/05/2014

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 IR: 11April2014
Date: Friday, April 11, 2014 3:47:00 PM
Importance: High

Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request:

1. **In your 4/1/2014 amendment (Response to FDA filling comments), you indicated that you will incorporate a particle size method and particle size distribution specification for the (b) (4) drug substance. Submit updated drug substance specification together with the particle size method details and validation, and the justification for the particle size distribution specification.**

2. **In your 4/1/2014 amendment (Response to FDA filling comments), you proposed to reduce the specifications for (b) (4) to NMT (b) (4)% and for (b) (4) to NMT (b) (4)% in the drug product at release and throughout the shelf-life. Submit revised drug product specification to incorporate these changes. In addition, revise the drug substance specifications to reduce the limit for (b) (4) to NMT (b) (4)% as well so that it is in line with the limit for the same impurity in the drug product.**

As we are approaching the midpoint for this review cycle, an expedited response to this IR would be greatly appreciated. Please respond via email as soon as possible, preferably before COB April 17, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

From:	Darkwah, Mavis
To:	frashkovsky@eagleus.com
Subject:	NDA 205579 IR: 11April2014
Date:	Friday, April 11, 2014 9:24:00 AM
Importance:	High

Foma,

Please refer to your NDA 205579 and respond to the information request below:

Information Request:

We are concerned with the in vivo dissolution of the nanoparticles of your product. In vitro dissolution would provide valuable information in this regard. Please provide the following:

1. **In vitro dissolution data using lower** (b) (4) **concentrations (including** (b) (4) (b) (4)**)**
2. **In vitro dissolution data in human plasma at lower rotation speeds, such as 50 rpm, 75 rpm and 100 rpm.**

As we are approaching the midpoint for this review cycle, an expedited response to this IR would be greatly appreciated. Please respond via email as soon as possible, preferably before COB April 17, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request
Date: Tuesday, April 08, 2014 3:50:00 PM
Importance: High

Dear Foma,

Please provide responses to the information request below:

Information Request

Once the 4 subjects who experienced treatment related AEs without an assigned relevant treatment (TRTR) have had their treatment identified, provide the following:

1. **Update the analysis datasets to include the TRTR information for those subjects.**

2. **Modify your ISS safety datasets (e.g., datasets such as ADAE, AECM) but not ADSL to include an additional column, TRTR CLASS, which lists the TRTR drug without the dose, i.e., it will contain either Ryanodex, Dantrium or Placebo for each adverse event. This will allow analyses of the AEs based on relevant treatment drugs without regard to the dose.**

As we are approaching the midpoint for this review cycle, an expedited response to this IR would be greatly appreciated. Please respond via email as soon as possible, by COB April 14, 2014, and follow with an official submission to the NDA

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

From: Darkwah, Mavis
To: frashkovsky@eagleus.com
Subject: NDA 205579 Information Request: 28March14
Date: Friday, March 28, 2014 3:03:00 PM
Importance: High

Dear Foma,

Please respond to the information request below:

Information Request:

1. **In the revised ISS database, there were four subjects for whom there was no treatment (TRTR) that was assigned to their adverse event. Provide the TRTR for these subjects or an explanation why TRTR cannot be or should not be assigned. All are included in the safety population. These subjects were:**
   a. **EGL-DANTROLENE-1201-001-0064**
   b. **EGL-DANTROLENE-1201A-28525**
   c. **EGL-DANTROLENE-1201A-32723**
   d. **EGL-DANTROLENE-1201A-48667**

2. **There are columns labeled AEDECOD and AEPT (which contains no data). Confirm whether the two columns were to refer to the same information and AEDECOD was the column ultimately used to report the MedDRA coded preferred terms, or whether AEPT was to serve another purpose.**

3. **For each of the amendments made to the two clinical protocols, how many subjects had been enrolled and treated with study drug at the time the amendment went into effect?**

Respond via email as soon as possible, by April 2, 2014 . And follow with an official submission to the NDA.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
04/21/2014

From: Darkwah, Mavis
To: "Foma Rashkovsky"
Subject: RE: NDA 205579 Advice/Information Request
Date: Thursday, March 13, 2014 4:50:00 PM
Importance: High

Dear Foma,

Please provide a response to the information request below:

Information request:

Create a table for the protocol deviation related to using the weaker hand for assessment of grip strength. In the table provide the unique subject ID, study number, treatment, and whether the strength assessment was made using the same hand before and after the treatment was administered.

Please respond to me via email by COB Monday, March 17, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Monday, March 10, 2014 4:24 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Advice/Information Request

Mavis,

Our responses to the 2 questions below are as follows:

Response to question 1:
For datasets ADAE, ADCM, ADEG, ADEX, ADLB, ADPC, ADPP and ADVS (sent to FDA on 5 March 2014), the treatment listed under variable TRTR (relevant treatment) is the variable which attributes the test result or event to: before study treatment (e.g. field is blank) or after study treatment (e.g. placebo or dantrolene sodium; by period as applicable). TRTR is derived from the comparison of the test result or event time/date with study treatment time/date.

Response to question 2:
The define file (*.pdf & *.xml formats; sent to FDA on 5 March 2014) reflects integration of all clinical data, as it relates to combining analogous analysis datasets from study portions 1201 (CCD) and 1201a (WCT).

Please note that due to integration of the data from 2 studies in our last response (3/5/2014) the datasets and Define files were placed in a new location in section 5.3.5.4 under ISS folder as new files.

An official submission to the NDA will be submitted tomorrow.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, March 10, 2014 8:59 AM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Advice/Information Request
Importance: High

Dear Foma,

Please respond to the additional information request below:

Information Request:

1) **Please confirm that, in the Basic Data Structure Datasets that contain more than one entity per subject (AE, Vitals, etc), the treatment listed under TRTR (relevant treatment) is the one to which you are attributing the row or event. If this is not the case, which column contains that information in each dataset.**

2) **Did you amend or replace your Define file to reflect your recent changes? If not please resubmit this file.**

Please respond to me via email by COB tomorrow, March 11, 2014, and follow with an official submission to the NDA.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Wednesday, February 19, 2014 9:04 AM
To: Darkwah, Mavis
Subject: RE: NDA 205579 Advice/Information Request

Dear Mavis,

We will submit the datasets as requested.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, February 19, 2014 8:25 AM
To: Foma Rashkovsky
Subject: RE: NDA 205579 Advice/Information Request

Dear Foma,

I have the following additional comments/advice from the team:

Please follow the following conventions for the addition of treatment arms to datasets such as AEs, vitals, etc...

1. **If an event occurs between 2 treatment arms, the one given prior should be selected as the relevant treatment**
2. **If an event occurs following the final treatment, that treatment should be assigned as the relevant treatment**

Submit all revised datasets as soon as possible, however no later than March 7, 2013.

Regards,

Mavis

From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Friday, February 14, 2014 3:13 PM
To: Darkwah, Mavis
Cc: Foma Rashkovsky
Subject: RE: NDA 205579 Advice/Information Request

Dear Mavis,

The following is the content of our proposed response:

Thank you for the follow up description of the information requested per our February 5th teleconference, and for the advice provided in the email below. Based on the input from the Agency, and on discussions with our consultants and vendors, Eagle will provide analysis SAS datasets (in SAS Xport Transport format) to include and integrate data from both study portions (1201 & 1201a for sites CCD & WCT, respectively) as follows:

adsl - Subject Level Analysis Dataset (using a 'one row per subject' format as prescribed and following a format that describes relationship between treatment and each unique event in our safety datasets)
adae - Adverse Events
adcm - Concomitant Medications

adeg - Electrocardiograms
adex - Exposure
adlb - Laboratory Tests (Clinical Chemistry, Hematology, Coagulation, Urinalysis)
adpc - Plasma Concentrations (dantrolene, 5-hydroxydantrolene)
adpp - Pharmacokinetic Parameters (dantrolene, 5-hydroxydantrolene)
advs - Vital Signs. Vital signs include blood pressure, pulse rate, respiratory rate, as well as oxygen saturation measurements either obtained by pulse oximetry or arterial blood gas measurements.

A define file and study data Reviewer's Guide will accompany the datasets.

Eagle would also like to work with the Agency by providing any necessary assistance via email, or telephone communications, to keep the review process moving forward.

Please confirm/advise if the datasets proposed for our response are acceptable.

Foma

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, February 10, 2014 4:02 PM
To: Foma Rashkovsky
Subject: NDA 205579 Advice/Information Request

Dear Foma,

As discussed in the teleconference, please refer to your NDA 205579 and respond to the information request/advice below:

> **Information Request:**
>
> Provide datasets that integrates your two studies (or study portions) 1201 and 1201A. You should do this for ally safety, exposure and disposition related datasets. Per our discussion, you will be supplying these as Analysis Datasets. Therefore you should also provide an integrated ADSL dataset that has one row per subject. If there are crossover study subjects or any with more than one randomized treatment, you can include the treatment sequence in the ADSL set BUT you should omit the treatment **arm** from the ADSL, and include a treatment variable column for all of your other datasets that record events (e.g., AEs, conmeds, vitals). This will provide the exact treatment for each unique event in your safety datasets.

Regards,

Mavis

Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER/OND/ODE II
Ph: (240) 402-3158

Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
03/14/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 105411
NDA 205579

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Eagle Pharmaceuticals, Inc.
50 Tice Boulevard
Suite 315
Woodcliff Lake, NJ 07677

ATTENTION: Foma Rashkovsky
Senior Director, Regulatory Affairs

Dear Mr. Rashkovsky:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA) dated January 21, 2014, received January 22, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dantrolene Sodium, Suspension for Injection, 250 mg/vial.

We also refer to:

- Your correspondence to your IND, dated and received August 16, 2013, requesting review of your proposed proprietary name, Ryanodex
- Your correspondence to your NDA, dated and received January 30, 2014, requesting review of your proposed proprietary name, Ryanodex

We have completed our review of the proposed proprietary name, Ryanodex and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 30, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Mavis Darkwah, Regulatory Project Manager, in the Office of New Drugs at (301) 402-3158.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
02/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 105411

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
470 Chestnut Ridge Rd
Woodcliff Lake, NJ 07677

Attention: Foma Rashkovsky
Senior Director of Regulatory Affairs

Dear Mr. Rashkovsky:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ryanodex (dantrolene sodium) suspension for injection.

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2013. The purpose of the meeting was to clarify open items from previous FDA communications, and to discuss the format and content of the Ryanodex NDA.

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

If you have any questions, call me at (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Mavis Y. Darkwah, Pharm.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: August 7, 2013, 2:00 PM
Meeting Location: Bldg. 22, Room 1313

Application Number: IND 105411
Product Name: Ryanodex (dantrolene sodium) suspension for injection
Indication: Prevention and treatment of malignant hyperthermia
Sponsor/Applicant Name: Eagle Pharmaceuticals, Inc.

Meeting Chair: Christopher D. Breder, M.D., Ph.D., Clinical Team Leader, Anesthesia drugs, DAAAP

Meeting Recorder: Mavis Darkwah, Pharm.D., Regulatory Project Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, M.D.	Division Director
Rigoberto Roca, M.D.	Deputy Division Director
Christopher D. Breder, M.D., Ph.D.	Clinical Team Leader
Arthur Simone, M.D., Ph.D.	Clinical Reviewer
Olen Stephens, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Team Lead, ONDQA
Edwin Jao, Ph.D.	CMC Reviewer
Adam Wasserman, Ph.D.	Pharmacology/Toxicology Team Leader
Jay Chang, Ph.D.	Pharmacology/Toxicology Reviewer
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Okpo Eradiri, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Janice Derr, Ph.D.	Acting Biostatistics Team Leader, Division of Biometrics II
Susan McDermott, M.D.	Medical Officer Team Leader, OCTEC
Rosemary Roberts, M.D.	Director, OCTEC
Andrea Vincent, Pharm.D.	Project Manager, OCTEC
Vicky Borders-Hemphill, Pharm.D.	Safety Evaluator, DMEPA
Diana Walker, Ph.D.	Senior Regulatory Project Manager
Mavis Darkwah, Pharm.D.	Regulatory Health Project Manager
Sponsor Attendees	**Title**
Paul Bruinenberg, M.D.	Chief Medical Officer, Eagle Pharmaceuticals, Inc.

Reference ID: 3365076

Reference ID: 3602867

Steven L. Krill, Ph.D.	Chief Scientific Officer, Eagle Pharmaceuticals, Inc.
Mark Smith, Ph.D.	V.P. Preclinical Development, Eagle Pharmaceuticals, Inc.
Foma Rashkovsky	Sr. Director of Regulatory Affairs, Eagle Pharmaceuticals, Inc.
Brian Chanas	Associate Director, Pre-Clinical Development, Eagle Pharmaceuticals, Inc.
Peter Pitts	Regulatory Consultant, President, CMPI (Center for Medicine in the Public Interest)

BACKGROUND

The purpose of this meeting is to clarify open items from previous FDA communications, and to discuss the format and content of the proposed Ryanodex NDA. The Sponsor met with the Division on July 9, 2009, for a PIND meeting, and on January 26, 2011, for an End-of-Phase 2 meeting. The Sponsor intends to submit a 505(b)(2) application referencing NDA 018264, Dantrium IV.

The questions from the July 1, 2013, meeting package are shown below in *italic* font, the preliminary responses are in **bold font**, and the discussion is in regular font.

The preliminary comments were sent to the Sponsor on August 6, 2013. After introductions, the discussion focused on questions, 2, 7, and 10.

DISCUSSION

Question 1: *Are the proposed particle size distribution criteria acceptable?*

FDA Response to Question 1:

Your proposed control strategy for particle size distribution appears reasonable. Acceptability of the specifications will be determined during review of your NDA in the context of all submitted data.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 2: *Does the Agency agree with the proposed dissolution testing procedure and acceptance criteria?*

FDA Response to Question 2:

Your determination of the saturation solubility of dantrolene sodium in the dissolution medium and characterization of dissolution at earlier time points are acceptable. However,

Reference ID: 3365076

Reference ID: 3602867

your proposed dissolution acceptance criterion will be evaluated upon review of the totality of the *in-vitro* dantrolene dissolution data in the NDA. Take note of the advice comments below in presenting your biopharmaceutics data/information in the NDA.

The dissolution data and information to be included in your NDA should conform to the following general guidelines:

1. **Dissolution Test: Include the dissolution method development report supporting the selection of the proposed dissolution test. The report should include:**

    a. **Solubility data for the drug substance over the physiologic pH range**

    b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product – The testing conditions should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.**

    c. **The complete dissolution profile data (individual, mean, SD, profiles) for your product – The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).**

    d. **Data to support the discriminating ability of the selected dissolution method – In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). This is crucial since you may be using dissolution test to justify request for a biowaiver on the three lower strengths.**

    e. **Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.)**

2. **Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:**

    a. **The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution**

Reference ID: 3365076

Reference ID: 3602867

acceptance criterion of your product (i.e., specification-sampling time point and specification value).

b. **The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.**

c. **For your proposed product, the selection of the specification time point should be where Q=(b) (4)% dissolution occurs.**

Discussion:
The Sponsor requested clarification as to what types of data are required to support the discriminating ability of the selected dissolution method. The Division responded that the Sponsor should determine if changing critical manufacturing variables affect drug release and if the dissolution method is able to detect such effects. The Agency also clarified that the reference product (discussed in the FDA Response 2 -1d) refers to the target formulation, and not to the listed drug.

The Sponsor stated that they will provide the details of the in vitro dissolution test, along with complete dissolution profiles of the relevant batches (registration and clinical) utilized to support the proposed acceptance criteria. They will also provide a discussion of the relevant solubility information, and an appropriate method validation report. The Sponsor clarified that they have developed a single strength (250 mg/vial) lyophilized intravenous product and, thus, a biowaiver will not be requested.

Question 3: *Based upon the analysis and the explanation provided, does the Agency agree that monitoring the product for (b) (4) is not warranted?*

FDA Response to Question 3:

Given the high pH of the solutions during filling and after reconstitution, and that (b) (4) can also be leached out from the glass vials, it is recommended that you conduct a one-time study in which the (b) (4) content of the suspension 6 hours after reconstitution is measured. Conduct a safety evaluation based on this leachable study and if the content of (b) (4) is well below the safety threshold, it is acceptable not to monitor it for commercial batches.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 4: *Does the agency agree that the package of nonclinical safety studies is sufficient for NDA filing?*

Reference ID: 3365076

Reference ID: 3602867

FDA Response to Question 4:

Yes.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 5: *Does the Agency agree with the proposed location in the NDA for the swine data related to PIND #* [redacted] (b) (4)*?*

FDA Response to Question 5:

It is unclear how the data related to [redacted] (b) (4) **would be appropriate or supportive of the indication being pursued. In the absence of a sufficient justification, these data should be omitted from the NDA, unless a safety signal is detected that might have implications for the use of Ryanodex to treat malignant hyperthermia.**

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6: *In accordance with the Animal Rule, does the Agency agree with the proposed ISS and ISE SAP for demonstrated efficacy and safety in the swine MH model for NDA filing?*

FDA Response to Question 6:

For the purposes of the clinical review, the proposed SAPs are adequate. See the response to Question 7 regarding the use of the Animal Rule for your application.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 7: *Does the Agency agree that the pharmacokinetic and safety data generated by the Phase 1 study is sufficient for the NDA Filing?*

FDA Response to Question 7:

The Division has given further consideration to the options you have in selecting a regulatory path for the Ryanodex NDA submission. Based on the studies you have conducted to generate evidence of the product's safety and efficacy as compared to Dantrium, we believe that a 505(b)(2) submission would be a feasible strategy. The following response is predicated on the decision to take this approach.

Reference ID: 3365076

Reference ID: 3602867

I. **We did not see results of the pharmacokinetic endpoints from the ongoing PK study in the meeting package. Providing information on linearity of PK parameters and safety observations associated with the anticipated higher C_{max} with your product will help us understand your product's safety profile.**

II. **Include the following in the NDA submission:**

   a. **Bioanalytical method validation information for analytical methods used to analyze dantrolene in systemic circulation**

   b. **Descriptive statistics of dantrolene PK parameters – We realize bioequivalence cannot be achieved; however, a bioequivalence analysis for C_{max} and the AUC of dantrolene following Ryanodex administration compared to Dantrium should be presented.**

   c. **Electronic datasets**

III. **For a 505(b)(2) application not submitted under Subpart H or I, if the PK parameters of the new product are nearly identical to those of the referenced product, it can be inferred that the efficacy and safety of the two products should also be identical. Without the actual data, it is not possible to determine how well the PK characteristics of Ryanodex match those of Dantrium. If the PK profiles for the two products are not identical, or nearly so, additional information may be required. In this situation, one of the following two alternatives would apply:**

   a. **If dantrolene exposure with Ryanodex is less than with Dantrium, it raises the question as to whether Ryanodex is as effective as Dantrium, and evidence of efficacy would be required. With less exposure, it would be expected that Ryanodex poses less risk and, therefore, the amount of safety data required for the benefit-risk analysis would be similarly reduced.**

   b. **If dantrolene exposure with Ryanodex is more than with Dantrium, this would raise the question as to whether Ryanodex poses additional risk compared to Dantrium. The extent to which the C_{max} differed would determine the amount of safety data needed to adequately characterize the risk profile. Therefore, it will be important to justify the size of your safety database in terms of it being adequate to characterize the risk profile of Ryanodex. In this regard, drawing on the safety findings for the two products in your nonclinical studies, the known risks identified by the long history of Dantrium use, the extent to which the two products were similar in your safety assessments, and the extent to which safety was evaluated at the highest tolerated doses will be important components of your rationale for the size of the safety database. This rationale should be incorporated into the ISS.**

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Discussion:

The Division informed the Sponsor that the information in the meeting package was not sufficiently complete to allow adequate review, and asked the Sponsor to submit descriptive statistics of the dantrolene PK parameters following Ryanodex and Dantrium administration (average +/- SD for C_{max}, AUC, Vd, Kel, $T_{1/2}$, Clearance and median (range) for T_{max}) as soon as possible. The Sponsor was advised that the descriptive statistics and study results should be organized in table format in order to facilitate an efficient review of the submission. The Sponsor was also encouraged to submit figures with individual or mean-linear or log-linear dantrolene PK profiles following Ryanodex and/or Dantrium administration.

The Sponsor responded that the rate of drug administration (mg dantrolene sodium per minute) for Ryanodex is higher than that of Dantrium IV. However, overall systemic exposures (in terms of AUC) are comparable between products. A bioequivalence analysis for C_{max} and the AUC of dantrolene following Ryanodex administration, compared to Dantrium, will be conducted. If bioequivalence of either parameter is not demonstrated, the Sponsor proposed that the Integrated Summary of Safety (ISS), detailing the safety data generated for both Ryanodex and Dantrium IV over the clinical labeled dose range (1 to 10 mg/kg) in the (5) MH-susceptible swine studies of malignant hyperthermia, will be expanded to include:

a. Descriptive information from the pivotal nonclinical toxicology study [study '1773-012' 14-day repeat dose study in conscious (non-MH susceptible) Gottingen minipigs] within which the NOAEL of 30 mg/kg/day was established

b. Descriptive information from the evaluation of the effects of cumulative doses of Ryanodex, and non-aqueous dantrolene sodium solution(s), on the systemic hemodynamics in (non-MH susceptible) anesthetized farm swine (study '1773-016')

c. A comprehensive summary of the comparative clinical safety profiles of Ryanodex and Dantrium IV over the dose range of 1.0 to 2.5 mg/kg (generated in study 'EGL-Dantrolene-1201')

d. A review of the published safety data for Dantrium IV

e. An overall comparison of pharmacokinetic data between the nonclinical species and humans, including absolute exposure data and the derived safety margins

The Division informed the Sponsor that they will likely need additional human safety data as the number of subjects in the PK study is not adequate to characterize the risks associated with Ryanodex. The extent to which the PK profile of Ryanodex differs from that of Dantrolene will determine, in part, the size of the safety database. While knowing the AUCs for the two products is helpful, the higher C_{max} for Ryanodex might pose an additional risk, depending on the magnitude of the difference, and that would need to be determined prior to the NDA submission. Therefore, the Division suggested that, along with the detailed clinical pharmacology summary

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statistics and accompanying human subject safety data, submission of a summary of the animal histopathology data including a comparison to Dantrium would be helpful in making a safety database size determination. The Division received clarification that descriptive information from the evaluation of the effects of cumulative doses of Ryanodex and non-aqueous dantrolene sodium solution(s) on the systemic hemodynamics in (non-MH susceptible) anesthetized farm swine would come from the GLP study '1773-015', and not the non-GLP study '117-016' as noted by the Sponsor in Item b. above. The Division indicated that the above information should be submitted for review so that further advice regarding the safety database could be provided.

The Sponsor agreed to provide the requested information.

Question 8: *Is the proposed NDA content (TOC) acceptable to support review of this application?*

FDA Response to Question 8:

The proposed TOC is acceptable. Note that the use of literature to support a finding of safety or efficacy requires that the publications be included in the submission, and translated into English if necessary. The literature should be summarized, critiqued, and incorporated into the ISE or ISS as appropriate; it should not be merely cited. In addition, the weight placed on published animal and human studies is substantially increased if original protocols or source data are provided as well.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 9: *Based on the content of this application will Eagle be required to pay full user fee or just half the fee?*

FDA Response to Question 9:

The Federal Food, Drug, and Cosmetic Act (the Act) states that for applications that require clinical data (other than bioavailability or bioequivalence studies) for approval with respect to safety or efficacy, a full application fee is assessed as set forth in the annual Federal Register notice establishing the yearly fee rates (see sections 736(a)((1)(A) and (c)(4) of the Act). Please be aware that literature can be considered clinical data for user fee purposes, and you may find a full description of what constitutes clinical data for user fee purposes in FDA's guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, available on the Internet. Based on the previous questions noted above, we would expect clinical data with at least the safety information required for approval, if not data for efficacy as well. Because we expect clinical data with respect to safety or efficacy for approval, we would expect a full fee for this application.

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Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 10: *If Orphan Drug Status is granted by OODP after the NDA is filed, will this confer priority review of the NDA?*

FDA Response to Question 10:

The granting of Orphan Drug Status by OODP has no bearing on whether an application is granted a priority review. Refer to the draft guidance for industry,
Expedited Programs for Serious Conditions—Drugs and Biologics at:
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf) for additional information on the qualifying criteria for Priority Review designation.

Discussion:

The Sponsor asked for clarification on accelerated approval and priority review designation criteria, under the scenario that the Office of Orphan Products Development grants Ryanodex Orphan designation.

The Division reiterated that the designation of priority review is not dependent or related to the Orphan Drug designation. The Division further explained to the Sponsor that accelerated approval is an approval pathway for an NDA, based on surrogate markers that are reasonably likely to predict clinical benefit, and that priority review is a designation that refers to the timeline that would be used for the review of the NDA, as stated in the draft guidance, for a drug that treats a *serious condition* and, if approved, would *provide a significant improvement in safety or effectiveness*.

The Sponsor clarified that, in that case, they are interested in priority review designation, and believe that their product is clinically superior to the existing product. The Division stated that, at the time of original NDA or efficacy supplement submission, the Sponsor should request priority review designation and articulate why they believe they qualify for priority review. The Agency will review the request and inform the Applicant in writing of priority review designation by day 60 of the NDA review, or of a standard review designation by Day 74 of the review. The Division also advised the Sponsor that, while clinical superiority is one criterion that may help to support priority review designation, it should not be confused with fulfilling the requirements for supporting superiority claims for labeling and marketing.

The Sponsor was advised to review the draft guidance on accelerated approval and priority review designation provided in the preliminary response.

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Post-meeting Note:
The Sponsor received orphan designation on August 16, 2013.

Question 11: *If Orphan Drug Status is granted by OODP after the NDA is filed, will Eagle be eligible for a refund of the PDUFA fee?*

FDA Response to Question 11:

Under section 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (the Act), a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the Act (orphan designation) is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.

If an application qualifies for an orphan exemption, the applicant does not need to send FDA a written request. The applicant should simply notify FDA that it is claiming the orphan exemption when it completes and submits the User Fee Coversheet, Form FDA 3397. The User Fee Coversheet should be included with the application, and a brief statement claiming the orphan exception should be included in the cover letter.

Nevertheless, FDA is aware there are situations when, at the time of submission of an application, the applicant has not received orphan designation for the proposed product. If that is the case, the applicant should pay the appropriate fee and submit to FDA a written request for a refund of the application fee. The applicant can submit the written request for a refund when they submit the fee and application. The applicant does not need to wait for FDA to determine if the proposed product receives orphan designation. However, under section 736(i) of the Act, the applicant must submit the written request no later than 180 days after the fee is due, and the fee is due upon submission of the application (section 736(a)(1)(B) of the Act).

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

ADDITIONAL COMMENTS:

Division of Medication Error Prevention and Analysis (DMEPA):

We notice that the product is being referred to as Ryanodex in the pre NDA package. If you intend to use this name, please submit a Request for Proprietary Name Review to the IND or NDA. The appropriate regulatory pathway for a Request for Proprietary Name Review is through a separate submission to your application. Acceptability of the proposed proprietary name requires a promotional and safety assessment. DMEPA will perform such an assessment once we receive a formal Proprietary Name review request. Once the

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assessment is complete, we will issue a letter with the final determination for your proposed Proprietary Name. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Post-meeting Note:
The Sponsor submitted a Request for Proprietary Name Review to the IND on August 16, 2013.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

Discussion:

The Sponsor stated that, for pediatric dosing in the Dosage and Administration section of the package insert, they planned (b) (4) labeling language (b) (4),

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(b) (4). The Sponsor asked if they are still required to satisfy the PREA requirement since they plan to develop only a single strength of the drug (250mg/vial), and that the dose for pediatric patients will be the same as adults. The Division told the Sponsor that we will respond to this with a post-meeting note.

Post-meeting Note: Since your product was granted orphan designation on August 16, 2013, for the treatment of malignant hyperthermia, the requirements of PREA will not apply to your application. However, from a public health standpoint, an assessment of the safety profile of Ryanodex in pediatric patients would still be an important and desirable goal.

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. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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

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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.				

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature

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Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

1. The Sponsor agreed to submit a complete and detailed description of the PK study and safety data with descriptive statistics that include dantrolene PK parameters following Ryanodex and Dantrium administration (average +/-SD for Cmax, AUC, Vd, Kel, $T_{1/2}$, Clearance and median (range) for T_{max}). In addition, the Sponsor agreed to submit BE-type analysis for comparing C_{max} and AUC parameters of dantrolene following administration of Ryanodex and Dantrium. The Sponsor also agreed to provide a summary of the bioanalytical methodology.

2. The Sponsor agreed to submit a summary of the animal histopathology findings and a comparison to the human study results.

3. The Sponsor will identify the size and type of IV access used in the PK study.

4. The Division agreed to review the clinical pharmacology, animal histopathology, and human safety data information and to provide additional details on the size of the safety database necessary at the time of NDA filing.

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5. The Division agreed to provide a response to the Sponsor's questions on their PREA requirement via a post-meeting note.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

MAVIS Y DARKWAH
08/29/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

PIND 105411

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
470 Chestnut Ridge Rd
Woodcliff Lake, NJ 07677

Attention: Brenda Marczi, Pharm.D.
Vice President, Regulatory Affairs

Dear Dr. Marczi:

Please refer to your Pre-Investigational New Drug Application (PIND) for Ryanodex (dantrolene sodium) suspension for injection.

We also refer to the meeting between representatives of your firm and the FDA on January 26, 2011. The purpose of the meeting was to provide you with feedback on the questions in your December 14, 2010, meeting package, which were related to your preparations for completing studies necessary to support an New Drug Application (NDA) for your product.

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

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING

Meeting Date: January 26, 2011
Time: 12:30 PM EST
Location: White Oak Conference Room 3270
Application: PIND 105411
Regulatory Status: Pre-submission
Product: Ryanodex (dantrolene sodium) suspension for injection
Proposed Indication: Prevention and treatment of malignant hyperthermia
Sponsor: Eagle Pharmaceuticals, Inc.
Type of Meeting: Type B, End-of-Phase 2
Meeting Chair: Rigoberto Roca, M.D., Deputy Director
Division of Anesthesia and Analgesia Products (DAAP)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAP

Industry Representatives	**Title**
Brenda Marczi, Pharm.D.	VP, Regulatory Affairs, Eagle Pharmaceuticals, Inc.
Pui-Ho Yuen, PhD	Sr Dir, Pharmaceutical Development, Eagle Pharmaceuticals, Inc.
Gregg Stetsko, PhD	Chief Scientific Officer, Eagle Pharmaceuticals, Inc.
David Wells, PhD	Nonclinical, Eagle Pharmaceuticals, Inc.
Sri Sundaram, Ph.D.	Pharmaceutical Development, Eagle Pharmaceuticals, Inc.
(b) (4)	Statistical Consultant
FDA	**Title**
Bob A. Rappaport, M.D.	Director, DAAP
Rigoberto Roca, M.D.	Deputy Director, DAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAP
Jay Chang, Ph.D.	Pharmacology/Toxicology Reviewer, DAAP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAAP
Sheetal Agarwal, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader, OCPB
Danae Christodoulou, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Prasad Peri, Ph.D.	Branch Chief, ONDQA
Dionne Price, Ph.D.	Biostatistics Team Leader, Division of Biostatistics II, Office of Biostatistics
Paul Brown, Ph.D.	Pharmacologist, Office of New Drugs
Kim Compton	Senior Regulatory Project Manager, DAAP

Meeting Objective:
To provide the Sponsor with feedback on the questions in their December 14, 2010, meeting package, which were related to their plans for submission of an NDA for their product.

Background:
On January 24, 2011 (prior to the January 26, 2011, meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the Sponsor in their December 14, 2010, meeting package.

The meeting entailed further discussion of Questions 4, 5, 8, 10, 11, 15, and 16.

Presented below are the Agency's January 24, 2011, comments and responses to questions in the background meeting package, followed by a summary of relevant discussion that took place at the meeting itself. The Sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Meeting

Chemistry Questions

Question 1
Does the Agency agree that the level of Povidone K12 in Ryanodex® (dantrolene sodium suspension) is adequately qualified for safety, based on its use in Alkeran® for Injection, and that no other safety assessment is required to support the use of this ingredient in Ryanodex?

FDA Response
The level of Povidone K12 in Ryanodex is adequately qualified for safety based on the total daily intake of the excipient from the maximum recommended daily dose of the approved product Alkeran® for Injection. Therefore, no additional studies should be necessary to qualify the safety of Povidone K12. However, if serious adverse effects that can be clearly linked to this ingredient are noted during the review of the nonclinical toxicity studies, additional safety information for Povidone K12 may be necessary.

Discussion
There was no further discussion on this point.

Question 2
Based on ICH Q3B, Eagle screened impurities and degradants specified in the drug product for structural alerts for mutagenicity. A structural alert for mutagenicity for [redacted] (b) (4) *is present in* [redacted] (b) (4) *(degradant specified in the USP monograph; monitored in drug substance & drug product)* [redacted] (b) (4) *specified in the USP monograph; monitored in drug substance and finished product). As these alerts are present in both the active pharmaceutical ingredient and related substances, they do not represent any additional risk over what is present in marketed dantrolene sodium drug products (intravenous & oral formulations). Dantrolene sodium has produced positive results in the Ames S. typhimurium bacterial mutagenesis assay in the presence and absence of a liver activating system. Toxicity studies in animals provided evidence of low-grade carcinogenic activity of Dantrium® in the rat. The presence of an alerting structure that is shared with the parent structure indicates that* [redacted] (b) (4) *impurities that are qualified based on the known properties of the parent compound.*

Does the Agency have any comments on this DRAFT product specification?

FDA Response
The proposed specifications appear to be acceptable.
Also refer to response to Questions 4 and 5 for specific comments to particle size and dissolution specifications.

Discussion
There was no further discussion on this point.

Question 3
The particulate matter test method currently employed evaluates only foreign particles against the acceptance criteria in m USP <788>. A copy of the particulate matter test method is provided as Attachment 3 in meeting package. Because the drug substance particles are dissolved during sample preparation and, therefore, are not counted, this method only evaluates foreign particles [Note: the size distribution of the drug substance particles is evaluated by a light scattering method (see question 4 below)].

Does this satisfactorily address the Agency's concerns for monitoring and controlling foreign particulate matter?

FDA Response
Your proposed method for foreign particulate matter appears to be acceptable.

Discussion
There was no further discussion on this point.

Question 4
The particle size distribution of drug particles in Ryanodex is determined and controlled using a light scattering technique; in particular, the level of larger particles is controlled solely by limiting the volume distribution of particles greater than (b) (4) *to NMT* (b) (4) *%. A copy of the particle size test method is provided as Attachment 4. Briefly, the particle size distribution is determined using a laser diffraction particle sizing instrument (* (b) (4) *) using* (b) (4) (b) (4) *Particle size controls are performed using* (b) (4) *The sensitivity of detection of the* (b) (4) *particles in the product under the conditions of the test has been established at about* (b) (4) *%.*

Does the Agency agree that this is an appropriate and sufficient method and limit to control for larger drug particles in the drug product?

FDA Response
A well validated method with a proper reference would be acceptable for monitoring particle size distribution. However, your particle size specification for the drug product is not acceptable due to clinical safety concerns. An assessment needs to be made to determine the fate of the particles following administration.

An in vitro study assessing the rate at which the particles dissolve would likely provide a good starting point. If it can be shown that the particles dissolve on contact, i.e., before they would have an opportunity to lodge in an arteriole or capillary, the issue would be resolved. If it appears that some particles would possibly cause embolic events, the risk would need to be characterized for a worst-case scenario.

Discussion of Questions 4 and 5

The Sponsor noted that they proposed the same specifications in July 2009 and were told that they were acceptable, and that they were also told to propose testing methods. They are now seeking clarification regarding why the specifications are no longer acceptable. The Sponsor also shared a video of the dissolution test in a previous experimental buffer which indicated that the drug suspension is completely dissolved in the buffer solution in less than (b) (4).

The Division stated that our recollection of the discussion in July 2009 was that it might be difficult to measure certain characteristics of the product because it dissolved so quickly. Ideally the product will be fully dissolved before it is given to the patient, so the Division would like the Sponsor to provide some evidence that the product is dissolved before it goes into the vein, noting that such evidence would alleviate this concern. The Sponsor reiterated that the product is a suspension when reconstituted and that the drug dissolves when the product enters into the patient's bloodstream.

The Division stated that the dissolution test is a quality control (QC) test, but noted that it could also address a clinical concern; therefore, it is not simply a standard QC test, but a characterization test as well. The Sponsor should include information on how much drug goes into solution (at a certain pH), at what volume, and at what time point by testing different batches and submitting the results in their NDA.

The Division also noted that data from the toxicology studies might provide some evidence of safety. Specifically, if the drug product was prepared the way it is to be in the clinical setting, administered at doses much higher than those to be used clinically, and the histopathological examination revealed no signs of embolic events, then the data would strongly suggest that embolic events in humans would not likely be a safety concern. The Sponsor stated that they may be able to obtain an earlier time point for dissolution and will explore whether they can administer higher concentrations of the product in nonclinical studies or if it would lead to formulation issues.

Regarding particle size specifications, the Division stated that having not more than (b) (4) of particles greater than (b) (4) is acceptable, but it is not clear at this time how many particles are greater than (b) (4). It is best to have a (b) (4) distribution and acceptance criteria (e.g., D10, D50, D90). The Sponsor agreed to provide this distribution.

Question 5
A dissolution test has been added and is performed in a Dissolution Apparatus 2 as described in USP <711> Dissolution. To perform the dissolution test, each vial of Ryanodex is reconstituted with 5.0 mL water for injection and mixed vigorously to form a uniform suspension. The entire content of the vial is withdrawn and delivered quantitatively into a 900 mL of the dissolution medium (0.5% benzalkonium chloride in water). The paddle speed is set at 50 rpm and the temperature of the medium is controlled at 37.0 ± 0.5°C. At (b) (4) minutes, respectively, a 10 mL sample is withdrawn from each of six dissolution vessels. The sample is filtered through a (b) (4) and analyzed for dantrolene sodium content. The acceptance criteria is that dissolved amount of dantrolene sodium at the (b) (4) min time point should be not less than (b) (4) % of total dantrolene delivered. (A copy of the dissolution test method is provided as Attachment 5 of the meeting package).

Are the proposed test and acceptance criteria for the dissolution limit test acceptable?

<u>FDA Response</u>
The proposed dissolution test method appears to be acceptable. However, the proposed dissolution acceptance criteria are not acceptable. (b) (4) minutes is too long a time period from clinical safety perspective. Also see the response to Question 4 above.

<u>Discussion</u>
See discussion under Question 4.

Question 6
An evaluation of the extractables and leachables from the container closure system with Ryanodex has been conducted that is consistent with the FDA guidance document, "Container Closure Systems for Packaging Human Drugs and Biologics". This evaluation takes into account compendial testing and extractables information from the manufacturers of the container closure system (vial and stopper) as well as the stability data Eagle Pharmaceuticals has already generated on the lyophilized drug product and the reconstituted solution. Based on this analysis, there is sufficient information relating to extractables/leachables to establish the safety and compatibility of the container/closure system with our drug product without additional extractables or leachables studies being required (the evaluation report of extractables and leachables is provided as Attachment 6 of the meeting package).

Based on the explanation and evaluation provided herein, is Eagle's plan for evaluation of extractables/leachables acceptable for the NDA filing of Ryanodex?

<u>FDA Response</u>
The proposed strategy for the evaluation of extractables and leachables appears to be acceptable for the NDA filing.

<u>Discussion</u>
There was no further discussion on this point.

Question 7
Is Eagle's plan for container closure compatibility testing acceptable to the Agency?

FDA Response
The proposed container closure compatibility testing appears to be acceptable.

Discussion
There was no further discussion on this point.

Question 8
Does the Agency agree that the slightly (b) (4) *content of the API lots used in the registration batches does not impact the use of these batches as primary stability batches in our NDA?*

FDA Response
This appears to be acceptable. We recommend that the API with (b) (4) **content be monitored for degradation products during stability. The weight of the API should be based on anhydrous API for the formulation of the drug product.**

Discussion
The Sponsor noted that the weight of the active ingredient in Dantrium and in the USP monograph is based on the (b) (4) formulation. The Division indicated that the outlined approach would then be acceptable.

The Division noted that the drug product would be at a high pH in (b) (4) and that leachables (b) (4) are noted at that pH, so the Sponsor should monitor for these in their drug product. The Sponsor agreed to continue monitoring (b) (4) and leachables.

Question 9
Based on the proposed Table of Contents (provided as Attachment 1), are there any other items for CMC that the Agency will require for filing and approval of the NDA?

FDA Response
The proposed table of contents appears to be acceptable. We recommend the CTD format for submission.

Discussion
There was no further discussion on this point.

Nonclinical Questions

Question 10
Does the Agency agree with the doses and species selected for the nonclinical safety evaluation of Ryanodex?

FDA Response

The species and doses selected for the nonclinical safety evaluation of Ryanodex appear to be appropriate. However, note that the doses of Ryanodex suspension employed must be high enough to produce plasma dantrolene concentrations that exceed what is achieved in humans at the maximum recommended clinical dose. Ideally, the supportive safety studies would identify clear No Adverse Effect Levels, which provide adequate margins of safety for the proposed clinical dosing. Ultimately, the adequacy and sufficiency of the doses employed in the nonclinical toxicity studies will be determined upon review of the information.

Discussion

The Division emphasized that the nonclinical evaluation for Ryanodex should focus on demonstrating the safety of the product. This would necessitate pushing the dose in animals to achieve both toxic effects and plasma dantrolene concentrations that exceed levels observed in humans when dosed according to the proposed label. The Sponsor expressed their concern about whether they could achieve sufficiently high plasma dantrolene concentrations, even at maximum tolerated doses in the dog since this species appears to exhibit a relatively high clearance of the product, and studies using a comparator arm of Dantrium limit the equivalent dose of dantrolene that can be administered as Ryanodex.

The Division clarified that the highest dose of Ryanodex administered does not need to be linked to the amount of dantrolene which can be given as Dantrium. The goal is to exceed the human exposure and provide information on target organ toxicity and ideally identify a NOAEL at a lower dose which provides a safety margin. The Division suggested that the Sponsor explore other animal species if the exposure in the dog cannot exceed the human due to enhanced clearance or other factors.

The Sponsor proposed that healthy minipigs might be a better species in which to conduct such toxicity studies. The Division responded that either dog or minipig would be acceptable, provided that sufficiently high exposures could be achieved. The Division also informed the Sponsor that a clinical study would ultimately need to be conducted due to the limited information regarding the pharmacokinetics of dantrolene in humans from published literature and the absence of such information with Ryanodex. The Sponsor noted that, in clinical practice the product is to be dosed to effect, and not given as a single bolus at the highest recommended dose of 10 mg/kg. In light of this, the Sponsor asked whether it would be acceptable to base nonclinical safety margins using human pharmacokinetic (PK) values collected in such a setting. The Division reiterated that the main goal for the nonclinical studies is that toxic effects should be pursued in animals and, therefore, doses should not be limited to clinically therapeutic levels.

The Division recommended that a dose-range finding study be conducted to determine maximum tolerated levels and perhaps to gain toxicokinetic data. The Division added that the concentration of Ryanodex used in nonclinical toxicity studies should be equal to, or higher than, the clinical formulation to address potential local toxicity which could

occur with this formulation, as well as toxicity associated with dissolution of the suspension as discussed in Question #4 above.

Question 11
Do the completed studies provide an adequate basis for the nonclinical safety evaluation of Ryanodex?

FDA Response
Yes, the summaries of the completed studies appear to provide a reasonable basis for the nonclinical safety evaluation of Ryanodex. However, the adequacy and sufficiency of the completed studies will be determined upon review of the information. Refer to Nonclinical Question 10 regarding the adequacy of the dosing for the completed nonclinical safety studies.

Discussion
See Discussion under Question 10 above.

Question 12
Based on the proposed package insert and Table of Contents (provided as Attachment 1), are there any other nonclinical items that the Agency will require for filing and approval of this NDA?

FDA Response
The nonclinical information contained in the proposed package insert and Table of Contents appears to be sufficient for filing of this NDA. Whether the underlying data supports the safety, efficacy, and ultimately the approval of Ryanodex will be determined by a review of the information submitted.

Discussion
There was no further discussion on this point.

Clinical Questions

Question 13
Does the Agency agree with the doses selected for the MH swine study and corresponding proposed package insert (the Ryanodex package insert includes a recommendation of 2.5 mg/kg as initial dose rather than 1 mg/kg that is currently recommended in the Dantrium IV package insert.

FDA Response
Although your animal study did not investigate the full range of dosing that is currently prescribed for dantrolene, there does not appear to be any evidence that a 1 mg/kg dose of Ryanodex would be less efficacious than the 1 mg/kg dose of Dantrium.

As it is relatively easier to rapidly reconstitute and administer Ryanodex compared to Dantrium, starting with a 1 mg/kg dose and titrating to effect should be easy to accomplish without significant delay in terminating the MH episode but with the opportunity to assess the extent of effect thereby minimizing the total dose and possible the side effects of the treatment. Therefore, without a justification for doing otherwise, the label for Ryanodex, if it is approved, would include the 1 mg/kg initial dose.

Discussion
There was no further discussion on this point.

Question 14
Does the completed pivotal study provide an adequate basis for the evaluation of the efficacy of Ryanodex for filing of the NDA?

FDA Response
The overall design of the pivotal trial, i.e., blinded, placebo- and active-controlled, was appropriate for the evaluation of efficacy and would be suitable for filing purposes. The details of the protocol and the study results will be evaluated as part of the review process once the NDA is filed.

Discussion
There was no further discussion on this point.

Question 15
Does the Agency agree with the proposed ISS and ISE SAP planned for the swine clinical data?

FDA Response
The proposed ISE and ISS will summarize the efficacy and safety of Ryanodex across four studies. You state, "Descriptive summaries will be provided by treatment group without formal inferential statistics." While this may be appropriate based on the small sample sizes, we remind you that the main purpose of the ISE is to explain how the results of the individual studies support the efficacy of your product.

Discussion
The Division stated that the response was meant to remind the Sponsor that, while pooling of the data may be acceptable, the ISE should provide quantitative and qualitative evidence that, based on the collection of animal studies, Ryanodex will be effective in the treatment of malignant hyperthermia when used in the clinical setting in accordance with the proposed labeling. In this regard, data from studies may be pooled, if appropriate, or presented separately. In addition, the similarities and differences between Ryanodex and Dantrium that were observed in studies comparing the two should be described and discussed in this section.

The Division also stated that the proposed plan for the ISS, including descriptive statistics and side-by-side comparisons and analysis of this product versus Dantrium, was acceptable. In this section, the case should be made that Ryanodex is safe when administered in accordance with the proposed labeling, and any differences in the safety profile between Ryanodex and Dantrium should be identified and discussed.

General Questions

Question 16
Based on all of the information provided above, does the Agency require any additional studies for the filing and approval of this 505(b)(2) NDA?

FDA Response
As indicated at the PIND meeting on July 23, 2009, clinical studies may be required for NDA submission following the Division's review of the animal study findings.

After a preliminary review of the data obtained in your pivotal efficacy study in the MH swine, it appears that there may be differences in the PK characteristics of dantrolene when administered as Ryanodex and Dantrium formulations. Since the two formulations differ significantly in terms of drug concentration leading to different total infusion time and total volume of infusion, it is important to characterize a safe dosing regimen in humans. Therefore, a single-dose study in humans needs to be conducted. The study should compare the PK and safety of Ryanodex (and its major metabolite, 5-hydroxydantrolene) to that of Dantrium. The PK findings will be used to verify whether the toxicology studies and animal efficacy study support the proposed upper limit of dosing in humans. The safety data will provide important information on whether Ryanodex has safety profile characteristics that need to be considered by clinicians when selecting an antidote for a given patient, both in the setting of prophylaxis and of treating MH episodes.

As there have been side effects reported in the administration of Dantrium to healthy volunteers (e.g., decrease in grip strength, weakness of leg muscles, especially walking down stairs, lightheadedness and difficulty swallowing and choking), one of two approaches may be taken for the clinical study.

Ideally, subjects could be drawn from the population of patients presenting for surgery who will need MH prophylaxis at the time of their operation. The PK and safety data from this population would reflect that of clinically relevant dosing. The benefits these subjects will gain from the dantrolene therapy would outweigh the risks for both treatments, assuming the animal studies for Ryanodex support the dose to be used.

Alternatively, healthy volunteers could be evaluated; however, doses less than those to be used in the clinical setting would likely be required to minimize the risk to the subjects for whom there will be no benefit from exposure to the drug products. The PK data from this population will resolve the issues described above, but the safety data may be less meaningful due to the reduction in dose. The alternative approach

should be used if the time to recruit patients requiring prophylaxis would be prohibitively long.

It is possible that this application may require the input of an Advisory Committee to obtain expert feedback regarding the adequacy of the animal and human data for supporting findings of safety and efficacy.

Discussion

The Division noted that it is important, from the clinical perspective, to establish whether there are differences between Ryanodex and the currently approved product. Such differences, if they exist, could be important in deciding which product should be used for any particular patient and would, therefore, constitute an important aspect in the labeling of Ryanodex. In this regard, it is important to characterize the safety profile for doses at least up to the maximum cumulative dose of 10 mg/kg. The animal toxicology data will be most useful if the studies involve dosing to toxic levels and if human PK data is collected to allow exposure comparisons and estimates of safety margins.

The Division noted that doses in excess of 10 mg/kg may be used in the clinical setting, if the malignant hyperthermia episode has not been broken despite administration of the highest labeled dose. In such situations, there are no alternative therapies and to cease giving dantrolene would likely result in the patient's demise. Understanding the risks associated with either Dantrium or Ryanodex at doses of at least 10 mg/kg allows the clinician to anticipate potential adverse events with appropriate monitoring and therapies. Knowing the safety margin associated with Ryanodex at doses of 10 mg/kg, or higher, constitutes an important aspect of characterizing the product's safety profile; it also constitutes an advancement in the safe and efficacious use of dantrolene to treat malignant hyperthermia. Although explorations of safety above the 10 mg/kg dose would be useful, they would not be required for an NDA.

Regarding the design of the PK study, the Division was willing to accept data from lower doses, i.e., less than 10 mg/kg, recognizing that the pharmacokinetics may not be linear. The Sponsor confirmed that they did not observe dose linearity of the product in studies conducted in the pig.

The Division stated that one of the purposes of the human PK study is to ascertain the applicability of the toxicology results from animals to humans, as well as to help characterize tolerability of the product. Since the product is used both for prevention and treatment of the condition, healthy people will likely be exposed to it, so all safety concerns will need to be delineated. In the human PK study, the Sponsor should monitor for changes that occur in vital signs, ECG, hematology, chemistry, coagulation parameters, and place special emphasis on neurologic assessments for adverse reactions observed with the administration of Dantrium. The study does not need to be sized to yield a typical safety database of more than 300 subjects, but should be sized to collect the necessary PK information and to yield meaningful information regarding safety and tolerability.

If any safety concerns are identified in the study, it will be useful to note whether they are the same or different from those seen with the approved product. If the Sponsor observes any problems with their product not seen with Dantrium, they will need to examine those further.

When selecting the population to be studied, it was agreed that the Sponsor may conduct a survey to determine if they could even obtain the necessary number of patients requiring prophylactic treatment needed for the study and, thereby, justify the use of a to-be-labeled dose, as the subjects would obtain a benefit from the drug that would likely outweigh any known risks. Alternatively, healthy volunteers could be studied starting with a below-labeled dose and increasing it, or start with a labeled dose provided there is safety data to support it. The Sponsor indicated that they would examine which approach is more feasible.

The human PK study will need to be conducted under an IND, which will require an assessment of the safety of the proposed protocol within 30 days of submission. The Division agreed that it would make every effort to also provide feedback regarding the other aspects of the study in a timely fashion considering the role this study will play in the NDA submission.

Question 17
Does the Agency agree that the proposed Table of Contents (provided as Attachment 1) lists all studies (no clinical studies in humans) and sections of Module 5 that will be required for the NDA?

FDA Response

According to our electronic submission module 4 and 5 subject matter experts the following is recommended:

> **An animal efficacy study can be considered a nonclinical study of primary pharmacodynamics (Module 4.2.2.1). The primary location should be in Module 4 and then provide a leaf reference under 5.3.5.4 (no attribute for species is necessary under 5.3.5.4). Since it's not a controlled or uncontrolled study, placing a leaf reference under 5.3.5.4 is more appropriate instead of under 5.3.5.1.**

Also, as a general rule, only attributes which are called for in the specifications should be provided.

Provide attributes for module 4 and 5 studies as per page 5 and 6 of the eCTD Backbone File Specification for Study Tagging Files 2.6.1 [PDF] (6/3/2008) http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf which states

> **C. Category Element**
> **The *category* element provides an additional level of study organization not currently provided by the eCTD DTD. This element is only relevant for studies provided in the specific CTD sections cited below.**

Page 5 ICH eCTD STF Specification V 2.6.1 3-June-2008
• 4.2.3.1 Single dose toxicity (grouped by species and route of administration)
• 4.2.3.2 Repeat dose toxicity (grouped by species, route of administration, and duration if applicable)
• 4.2.3.4.1 Long term [carcinogenicity] studies (grouped by species)
• 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication (grouped by type of control)

If you provide a high level reviewer's guide as an overview of the application in the first level submission type such as an original-application, providing a reference and link to the study can also be helpful.

Discussion
There was no further discussion on this point.

The Sponsor summarized their understanding of the meeting as follows (includes action items)

1. **The Sponsor understands that they should provide a separate characterization test for the time that the product dissolves in medium at a certain pH in addition to quality control dissolution test.**

2. **The Sponsor understands that the Division recommend that the Sponsor look at a (b) (4) point specification for particle size and provide data on how many particles are greater than (b) (4).**

3. **There was agreement that the calculation of the weight of the API may be based on the (b) (4) formulation as it is with Dantrium and in the USP monograph.**

4. **The Sponsor will examine ways to increase the dose in animal models to achieve toxic levels and to provide an assessment of the margin of safety that exists, if any, for the proposed human doses. The Division reminded the Sponsor that observation of toxicity should be the goal in those studies.**

5. **The Sponsor understands the purpose and proper makeup of the ISS and ISE.**

6. **The Sponsor understands the need for the human PK study and what the Division is looking for in the design of such a study. They will determine which approach is most feasible--either a study involving the use of Ryanodex for prophylaxis in malignant hyperthermia susceptible patients scheduled for surgery, or one in healthy volunteers, starting with a low dose and increasing as appropriate. They understand that such a study needs to be conducted under an IND. They understand that they will get feedback on the safety aspects of the study by way of its review as a new IND and that the Division will also make an effort to otherwise review and provide feedback on the study in a timely manner since it is pivotal to the product's development.**

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/s/

KIMBERLY A COMPTON
02/17/2011