CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208956 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Triptodur Established/Proper Name: triptorelin Dosage Form: extended-release injectable suspension, for intramuscular use		Applicant: Arbor Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A
RPM: Jennifer Johnson		Division: Division of Metabolism and Endocrinology 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:

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 June 29, 2017	☒ 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, 505(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.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5
(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

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

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: 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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval letter (June 29, 2017)
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 (Refer to final approved labeling attached to approval letter issued on June 29, 2017)
• Original applicant-proposed labeling	☒ Included (August 29, 2016)
❖ 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 (Refer to final approved labeling attached to approval letter issued on June 29, 2017)
• Original applicant-proposed labeling	☒ Included (March 24, 2017)
❖ 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 (final diluent label submitted May 31, 2017; final vial, kit carton and carton labels submitted June 12, 2017)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	 November 21, 2016 November 14, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: November 10, 2016 DMEPA: April 26 and June 12, 2017 DMPP/PLT (DRISK): June 21, 2017 OPDP: June 19, 2017 SEALD: ☒ None CSS: ☒ None Product Quality May 30, 2017 Other: DPMH (PLLR) May 26, 2017
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	November 10, 2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o 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: Orphan designation was granted for this product and indication on August 20, 2012 (designation request #12-3760)	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ 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)	N/A
❖ 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 December 3, 2015
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• 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 focused milestone meetings) *(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)*	June 29, 2017
Cross-Discipline Team Leader Review *(indicate date for each review)*	June 29, 2017
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review (See CDTL review June 29, 2017)
• Clinical review(s) *(indicate date for each review)*	June 5, 2017; October 24, 2016
• 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)*	See page 77 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	OSE/DPV-1: April 6, 2017 CDRH/OC/DMQ: January 9 and June 1, 2017 CDRH/ODE/DAGRIP/GHDB: June 7, 2017
❖ 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)*	April 19, 2017
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)*	May 19, 2017; October 25, 2016

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

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)*	May 25, 2017 October 25, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
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)*	May 25, 2017 October 19, 2016
❖ 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
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	May 30, 2017 October 26, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(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)*	May 30, 2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable: April 28, 2017 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ 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	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

JENNIFER L JOHNSON
07/05/2017

From: Allison Lowry
To: Johnson, Jennifer
Subject: RE: NDA 208956 (Triptodur): Final PI and Medication Guide
Date: Thursday, June 29, 2017 1:35:26 PM

Thank you, Jennifer! We agree to the PI and Med Guide and I'll get these submitted asap.

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, June 29, 2017 1:29 PM
To: Allison Lowry
Subject: RE: NDA 208956 (Triptodur): Final PI and Medication Guide

Hi Allison,

I have discussed with my team, and we agree with your two proposed edits, which I've incorporated into the attached PI.
Please reply with your agreement on the final agreed upon PI and Medication Guide, and submit officially to the NDA as soon as possible.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Thursday, June 29, 2017 10:34 AM
To: Johnson, Jennifer
Subject: RE: NDA 208956 (Triptodur): Final PI and Medication Guide

Hi Jennifer,

Under Highlights, Adverse Reactions, the team inquired if we could say (like the Lupron label): "In clinical trials for TRIPTODUR, the most common adverse reactions (b) (4) 4.5% (b) (4)

(b) (4) that is carried over from the original annotation that was submitted. Can we delete that?

If accepted, can these changes be incorporated into the final PI? Or, if accepted, do I need to send it quickly? I can attach an annotated version (from FDA clean copy) via email , if needed.

Thanks for your help!
Allison

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, June 29, 2017 8:10 AM
To: Allison Lowry
Subject: RE: NDA 208956 (Triptodur): Final PI and Medication Guide

Thanks, Allison!
Jennifer

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Thursday, June 29, 2017 6:31 AM
To: Johnson, Jennifer
Subject: RE: NDA 208956 (Triptodur): Final PI and Medication Guide

Hi Jennifer,

I am confirming with the team and will circle back this a.m.

Thanks!
Allison

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Wednesday, June 28, 2017 11:45 PM
To: Allison Lowry <Allison.Lowry@ArborPharma.com>
Subject: NDA 208956 (Triptodur): Final PI and Medication Guide

Hi Allison,

Thank you for sending your most recent version of the label yesterday.
Please find attached our edits to the label and Medication Guide, in tracked changes and clean Word versions.
We consider this the final label and MG to be attached to the action letter.
Let me know if your team agrees, and if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
06/29/2017
Final agreed-upon PI and MG

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Final PI and Medication Guide
Date:	Wednesday, June 28, 2017 11:45:11 PM
Attachments:	Triptodur medication-guide-clean 28 June 2017.docx Triptodur medication-guide-tracked-changes 28 June 2017.docx Triptodur PI Final FDA edits-06-28-2017-annotated.docx Triptodur PI Final FDA edits-06-28-2017-clean.docx

Hi Allison,

Thank you for sending your most recent version of the label yesterday.
Please find attached our edits to the label and Medication Guide, in tracked changes and clean Word versions.
We consider this the final label and MG to be attached to the action letter.
Let me know if your team agrees, and if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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Food and Drug Administration
Phone: (301) 796-2194
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jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
06/28/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Latest FDA edits to PI
Date:	Monday, June 26, 2017 6:07:26 PM
Attachments:	Triptodur PI-annotated FDA edits 26 June 2017.docx Triptodur PI-clean FDA edits 26 June 2017.docx

Dear Allison,

Thank you for sending your latest PI last Friday. Please find attached our tracked changes and clean versions of the PI.
We ask that you make any subsequent changes to the clean version and send back to us by tomorrow.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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Food and Drug Administration
Phone: (301) 796-2194
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jennifer.johnson@fda.hhs.gov

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JENNIFER L JOHNSON
06/26/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): FDA edits to PI and MG
Date:	Wednesday, June 21, 2017 6:11:42 PM
Attachments:	TRIPTODUR NDA 208956 DMPP Medication Guide Marked Jun-2017.docx Triptodur PI FDA edits 21 June 2017 annotated.docx

Hi Allison,

Thank you for your and your team's time today during the teleconference.

As discussed, please find attached the latest versions of the PI and Medication Guide (which has been reviewed by our patient labeling group, and we concur with their edits). We kindly request a response by this Friday, June 23rd.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Wednesday, June 21, 2017 4:05 PM
To: Johnson, Jennifer
Subject: Re: NDA 208956 (Triptodur): Availability for brief teleconference Wed 6/21?

Thanks! We're here -

Sent from my iPhone

On Jun 21, 2017, at 3:59 PM, Johnson, Jennifer <Jennifer.Johnson@fda.hhs.gov> wrote:

> Hi Allison,
>
> We may be a few minutes late dialing into the meeting but we'll be there—talk to you soon.
>
> Thanks!
> Jennifer

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/s/

JENNIFER L JOHNSON
06/21/2017

From: Johnson, Jennifer
To: "Allison Lowry"
Bcc: Johnson, Jennifer
Subject: NDA 208956 (Triptodur): Carton/container label revisions
Date: Wednesday, June 07, 2017 4:31:30 PM

Hi Allison,

I'm following up on your question. I've discussed with my team, and the diluent label is acceptable.

However, the carton and container labels need further revision to match our revisions made to the current PI draft.

Please revise as follows:

1. container and carton labels to state "TRIPTODUR (triptorelin) for extended release injectable suspension".
2. carton label to include the equivalency statement "triptorelin (base units)…22.5 mg, equivalent to triptorelin pamoate…31 mg".

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Monday, June 05, 2017 4:36 PM
To: Johnson, Jennifer; Galgay, Linda
Subject: RE: Out of office May 26-June 2

Hi Jennifer,

Welcome back and hope you had a nice time off! I did not circle back with Linda on the syringe label to ensure the reviewer concurred with our revisions. We made all
The requested revisions (submission sequence was 0016). Can you follow up when you get a chance?

Thanks!
Allison

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, May 25, 2017 3:55 PM
To: Allison Lowry; Galgay, Linda
Subject: RE: Out of office May 26-June 2

Hi Allison,

Thanks for checking in.
Assuming that you make all of our requested revisions, we don't anticipate having any further revisions.
Once you submit, Linda will send on to our colleagues who review carton/container labeling for their concurrence.
If they concur, those labels can be considered final for attachment to the action letter.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Thursday, May 25, 2017 2:48 PM
To: Galgay, Linda; Johnson, Jennifer
Subject: RE: Out of office May 26-June 2

Hi Jennifer and/or Linda,

I have a question that I'm hoping you can field. Regarding the syringe label, which is: **DILUENT STERILE WATER FOR INJECTION LABEL:**.

Comments were provided by the FDA team which we'll complete and submit next Wednesday (31st) as stated. I'm not sure if this is something you can answer now, but is it possible for the reviewer to relay if these will be the final changes on the Syringe label? Given the long lead times, we were hoping to place an order for them.

Thanks for your help!
Allison

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Galgay, Linda [mailto:Linda.Galgay@fda.hhs.gov]
Sent: Thursday, May 25, 2017 2:07 PM
To: Allison Lowry; Johnson, Jennifer
Subject: RE: Out of office May 26-June 2

Hi Allison,

I look forward to working with you.

Best regards,

Linda

Linda V. Galgay, RN, MSN
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-5383
Fax: 301-796-9712
linda.galgay@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Thursday, May 25, 2017 1:50 PM
To: Johnson, Jennifer
Cc: Galgay, Linda
Subject: RE: Out of office May 26-June 2

Thanks, Jennifer. Enjoy your time off!

Linda, I look forward to corresponding with you during the coming week and will keep all in the loop!

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, May 25, 2017 12:25 PM
To: Allison Lowry
Cc: Galgay, Linda
Subject: Out of office May 26-June 2

Hi Allison,

I will be out of the office starting Friday, May 26th through Friday, June 2nd.
During this time I will not have access to my email and my colleague Linda Galgay will be covering.
I have copied her on this email, and she may also be reached at 301-796-5383.
While I am away, could you please copy me on any emails that you send to Linda regarding Triptodur NDA 208956?
Let me know if you have any questions.

Thanks!
Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
06/08/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Enhanced pharmacovigilance request
Date:	Thursday, June 08, 2017 6:04:49 PM

Dear Allison,

Regarding NDA 208956 (Triptodur), we would like to inform you of our intention to include the following request in the action letter for this product, if approved:

> We request that for a period of 5 years from the U.S. approval date, you submit all cases of suicidal ideation and behavior, self-injury, or depression, (b) (4) reported with TRIPTODUR (triptorelin (b) (4) for extended-release injectable suspension as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of events of suicidal ideation and behavior, self-injury, depression, and (b) (4) reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of TRIPTODUR (triptorelin (b) (4) for extended-release injectable suspension as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of events of suicidal ideation and behavior, self-injury, depression, (b) (4) reported with TRIPTODUR (triptorelin (b) (4) for extended-release injectable suspension should also be provided in the periodic safety report.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C PBRER format, you will need to submit a formal waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs. You should ensure that your proposal does not result in any gaps in reporting.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

JENNIFER L JOHNSON
06/08/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Latest FDA edits to PI
Date:	Tuesday, June 06, 2017 12:12:08 PM
Attachments:	Triptodur PI FDA edits 6 June 2017 annotated.docx

Hi Allison,

Please find attached the latest FDA edits to the Triptodur PI. We ask that you review our comments sent in tracked changes format and accept those with which you agree. For any comments that you do not agree with, provide your justification in a comment box and provide your alternative language in tracked changes format. Clearly label your comment as "Applicant Comment."

We respectfully request a response by Thursday, June 8th.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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/s/

JENNIFER L JOHNSON
06/06/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): FDA revisions to PI and Medication Guide
Date:	Wednesday, May 24, 2017 4:42:32 PM
Attachments:	Triptodur PI FDA edits 24 May 2017.docx Triptodur Medication Guide FDA edits 24 May 2017.docx

Hello Allison,

For Triptodur NDA 208956 currently under review, please find attached our latest revisions to the PI and Medication Guide.

We respectfully request a response by next Tuesday, May 30th.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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/s/

JENNIFER L JOHNSON
05/24/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Carton/Container Labeling Comments
Date:	Tuesday, May 23, 2017 5:17:11 PM

Hello Allison,

For Triptodur NDA 208956, we have reviewed the carton and container labels submitted on August 29, 2016, and have the following comments and recommendations to be implemented prior to approval:

A. CONTAINER KIT LABEL

1. The lot and expiration numbers are missing. Ensure the expiration date conforms with the format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry, where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYY (e.g., FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g., FEB012020).

2. Revise the statement [redacted] (b) (4) on the container kit label contents section to "One Pre-filled Syringe of Diluent for Triptodur, 2 mL". This will highlight that the medication comes with a diluent and must be used for reconstitution before use.

3. Add "Do not freeze" with the storage information as currently presented this key information is missing.

B. CONTAINER VIAL LABEL:

1. Revise the route of administration from [redacted] (b) (4) to "For Intramuscular Injection". Dangerous abbreviations, symbols, and dose designations are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.

2. The barcode is in a horizontal position. Barcodes placed in a horizontal position may not scan due to curvature of the vial. We recommend reorientation of the barcode to a vertical position to improve scannability. Ensure the barcode is surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21CFR201.25(c)(1)(i).

3. Revise [redacted] (b) (4) to "For Reconstitution, Use Accompanying Diluent" as currently presented the statement is unclear and may cause confusion.

C. CARTON KIT LABELING:

1. Revise the content statement [redacted] (b) (4) to "One Pre-filled Syringe of Diluent for Triptodur, 2 mL". This will highlight the need to reconstitute before use.

2. Consider adding the cautionary statement "Reconstitute With Accompanying Diluent Before Use" to ensure this important information is not missed.

D. DILUENT STERILE WATER FOR INJECTION LABEL:

1. Revise the statement [redacted] (b) (4) as presented below to prevent confusion and ensure that that the diluent is not administered alone:

Diluent

For Triptodur for Injection

2. Revise the statement [redacted] (b) (4) to "For drug diluent use only – reconstitute as directed" to ensure this important information is not misinterpreted.

a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet]. FDA. April 2013 [cited 2017 April 19]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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/s/

JENNIFER L JOHNSON
05/23/2017
Carton/container labeling comments per DMEPA review 4/26/17

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	RE: NDA 208956 (Triptodur): Information Requests
Date:	Wednesday, May 17, 2017 4:31:58 PM

Hi Allison,

We have a follow-up information request:

You provided a 510(k) clearance letter for the referenced 510(k) submission (b) (4) (b) (4) packaged in the combination product. The 510(k) clearance letter will not authorize the Agency to reference information regarding the needle for your NDA submission. Please obtain a letter of authorization from (b) (4) for the 510(k) submission (b) (4)

We would appreciate a response at your earliest convenience.
Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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jennifer.johnson@fda.hhs.gov

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Monday, May 08, 2017 5:11 PM
To: Johnson, Jennifer
Subject: RE: NDA 208956 (Triptodur): Information Requests

Hi Jennifer,

Regarding item #3 below, I wanted to let you know that (b) (4) sent the results (which you may have already received via email) directly to you today. We'll also make note of that in our reply on May 10.

Thanks!
Allison

Allison Lowry
Director, Regulatory Affairs

Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, May 02, 2017 5:21 PM
To: Allison Lowry
Subject: RE: NDA 208956 (Triptodur): Information Requests

Thanks, Allison!
Jennifer

From: Allison Lowry [mailto:Allison.Lowry@ArborPharma.com]
Sent: Tuesday, May 02, 2017 5:11 PM
To: Johnson, Jennifer
Subject: RE: NDA 208956 (Triptodur): Information Requests

Thanks, Jennifer! We'll get this information to you on or before the due date.

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, May 02, 2017 3:20 PM
To: Allison Lowry
Subject: NDA 208956 (Triptodur): Information Requests

Dear Allison,

For NDA 208956 (Triptodur), we have the following information requests:

1. You referenced 510(k) submission (b) (4) ackaged in the combination product, while no authorization letter was provided. In order for the Agency to reference information regarding the needle, please provide a letter of cross-reference from (b) (4)

2. You provided specifications of Break up force and Gliding force for Water for Injection, while did not provide Break up force and Gliding force for reconstituted final drug product. Provide a justification that the specifications of Break up force and Gliding force for Water for Injection can be used for the reconstituted final drug product based on the drug uniformity and viscosity comparison with water, otherwise additional testing on the reconstituted final drug product may be necessary.

3. You provided quality control specifications for Sterile Water for Injection in 3.2.P.5. Control of Drug Product. Please contact the DMF holder and obtain the data for (b) (4) cap removal force and include (b) (4) cap removal force in the spec table, otherwise additional testing may be required.

4. Provide a detailed protocol of the dose accuracy study of lyophilized triptorelin pamoate

which you submitted in your Response to FDA Request-Study Quality Information dated February 24, 2017.

We respectfully request a response by close of business next **Wednesday, May 10th**.
Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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JENNIFER L JOHNSON
05/17/2017
IR from CDRH reviewer Rong Guo

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Information Requests
Date:	Tuesday, May 02, 2017 3:19:39 PM

Dear Allison,

For NDA 208956 (Triptodur), we have the following information requests:

1. You referenced 510(k) submission [redacted] (b) (4) packaged in the combination product, while no authorization letter was provided. In order for the Agency to reference information regarding the needle, please provide a letter of cross-reference from (b) (4)

2. You provided specifications of Break up force and Gliding force for Water for Injection, while did not provide Break up force and Gliding force for reconstituted final drug product. Provide a justification that the specifications of Break up force and Gliding force for Water for Injection can be used for the reconstituted final drug product based on the drug uniformity and viscosity comparison with water, otherwise additional testing on the reconstituted final drug product may be necessary.

3. You provided quality control specifications for Sterile Water for Injection in 3.2.P.5. Control of Drug Product. Please contact the DMF holder and obtain the data for (b) (4) cap removal force and include (b) (4) cap removal force in the spec table, otherwise additional testing may be required.

4. Provide a detailed protocol of the dose accuracy study of lyophilized triptorelin pamoate which you submitted in your Response to FDA Request-Study Quality Information dated February 24, 2017.

We respectfully request a response by close of business next **Wednesday, May 10th**.
Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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JENNIFER L JOHNSON
05/02/2017
IR from CDRH reviewer Rong Guo

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Information Request (Package Insert)
Date:	Friday, April 21, 2017 6:13:08 PM

Dear Allison,

We are continuing to review the package insert submitted to your NDA 208956 (Triptodur), and have the following request for further information.

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. We found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made. Please resubmit the following information by **May 7, 2017**:

• a review and summary of all available published literature regarding triptorelin use in pregnant and lactating women, and the effects of triptorelin on male and female fertility (include search parameters),

• a copy of each reference publication cited in the above literature reviews and summaries,

• a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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JENNIFER L JOHNSON
04/21/2017
IR from PMHS (PLLR consult review)

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, April 06, 2017 5:54 PM
To: 'Allison Lowry'
Subject: NDA 208956 (Triptodur): Clinical Information Requests

Dear Allison,

Regarding your NDA 208956 for Triptodur (triptorelin pamoate) currently under review, we have the following requests for information:

- An analysis of the risk for eye disorders, intracranial hypertension, and bone marrow/blood disorders with the use of triptorelin in all pediatric patients from the Debiopharm and Ipsen safety databases for triptorelin and the medical literature.
- A line listing and CIOMS (or MedWatch) reports of all pediatric cases of eye disorders, intracranial hypertension, and bone marrow/blood disorders.

We respectfully request that you submit this information to the NDA by April 24, 2017.

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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JENNIFER L JOHNSON
04/06/2017

March 7, 2017

From: Johnson, Jennifer
To: "Allison Lowry"
Bcc: Johnson, Jennifer
Subject: NDA 208956 (Triptodur): Request for product samples
Date: Tuesday, March 07, 2017 6:08:13 PM

Dear Allison,

Regarding NDA 208956 for your proposed Triptodur (triptorelin pamoate) for injectable suspension 22.5 mg product submitted on August 29, 2016, we request that you provide three (3) intend-to-market representative samples by Tuesday, March 14, 2017.

The samples may be sent to me at the following address:

Jennifer Johnson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3114
10903 New Hampshire Avenue
Silver Spring, Maryland
*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)*

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
03/07/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Request for Package Insert Revisions and Medication Guide
Date:	Friday, February 24, 2017 3:14:24 PM
Attachments:	NDA 208956 Original Proposed PI - FDA comments 22Feb2017.docx

Dear Allison,

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for triptorelin for (b) (4) suspension. We request submission of the following information **by March 24, 2017**.

While review of your application remains ongoing, we have become aware of postmarketing cases of seizures and serious psychiatric adverse events in central precocious puberty patients receiving GnRH agonists. We are sending the attached preliminary comments to your proposed Prescribing Information (PI) to incorporate this new safety information. Please note that we are deferring comment on the remainder of your proposed PI at this time.

In addition, we believe that the new safety information should be included in a Medication Guide. You should submit a revised PI and create a new Medication Guide that conforms to your proposed PI.

If your product is approved, you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided, per 21 CFR 208.24(d). You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- (b) (4) or
- "Dispense the accompanying Medication Guide to each patient."

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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JENNIFER L JOHNSON
02/24/2017

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Device-related information requests
Date:	Friday, February 24, 2017 3:40:19 PM

Dear Allison,

Regarding your submission, NDA 208956 (Triptodur), you need to demonstrate safety and effectiveness of the combination product, including the device constituent parts. In order for the Agency to complete the assessment of the safety and effectiveness of your proposed drug product, please provide the following:

1. Information from dosing accuracy studies, biocompatibility studies, and leachable/extractable studies are needed to support this NDA. Please state as soon as possible where this information can be found. If this information is provided through a referenced DMF, please provide the exact location within the DMF as well as the date that the information was submitted to the DMF. A detailed description of the expected information is included in the following text.

2. Provide the following information for the device included in the submission:

a. A description of the complete device, including individual device components, configurations, and packaging in its final form.

b. A document listing the design requirements specifications for the device constituents.

c. Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states.

d. Verification and validation of the following specific system attributes. If this information is within a device master file, please provide the exact location.

i. Accuracy of delivered dose

ii. Biocompatibility of system components commensurate with the level and duration of patient contact (see question 3 for additional biocompatibility comments)

iii. Compatibility of the DP vial, luer-lock adaptor, and syringe (i.e. fitment of the adaptor to vial, and syringe to the adaptor without leakage)

e. The lot release specifications for the essential performance requirements of the device constituent part of the proposed combination product.

3. Provide the location of the following information to address the biocompatibility of the device constituents of the combination product:

a. The leachables and extractables testing along with a toxicological risk assessment based on the intended patient population.

b. The biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. The biocompatibility evaluation should take into account the repeated use of the device, which includes the re-use of the each syringe. The biocompatibility evaluation should also take into account the drug that is being delivered. Please provide the location of the test summaries, test method (including sample preparation and acceptance criteria), and the full

test reports. The extractables and leachables testing may be used to address the systemic endpoints (e.g. acute and subchronic toxicity).

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
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/s/

JENNIFER L JOHNSON
02/24/2017

From: Lalmansingh, Anika
To: Allison Lowry
Cc: Johnson, Jennifer
Subject: NDA 208956 - Information Request, 2/8/2017
Date: Wednesday, February 08, 2017 1:54:57 PM
Attachments: image002.png

Information Request – CMC only

NDA 208956

Dear Ms. Lowry,

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for triptorelin for (b) (4) suspension. We request submission of the following information by **Wednesday, March 8, 2017**:

The following comments are specific to the cGMP requirements for your combination product:

Please note that for combination products manufactured under the CGMP drug operating system, you must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product; we refer you to the FDA Guidance "Current Good Manufacturing Practice Requirements for Combination Products; Final Guidance" (2017). To assist in the preparation of the summaries below related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, you are recommended the FDA Guidance "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff" (2003). As the NDA applicant, you are responsible for ensuring that a system is in place for the appropriate quality system controls covered for this application. (b) (4)

(b) (4)

(b) (4)

Kindly acknowledge receipt of this email.

Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356
anika.lalmansingh@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
02/08/2017
CMC IR sent by Anika Lalmansingh to sponsor via email on 2/8/17

From:	Johnson, Jennifer
To:	"Allison Lowry"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Clinical Request for Information
Date:	Tuesday, January 31, 2017 7:37:25 PM

Dear Allison,

For NDA 208956 (Triptodur) currently under review, we have the following information request.

Please provide complete patient narratives for Subject 280101 and Subject 630101. The narratives should include but not be limited to the following information: detailed medical histories, concomitant medications, laboratory results, and all adverse events (AEs) that occurred during the study. We are specifically interested in details regarding Psychiatric SOC AEs experienced by these patients. Provide your causality assessment of 5 episodes of anxiety in Subject 280101 and 1 episode of mood altered in Subject 630101.

We respectfully request a response by February 7, 2017.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
01/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208956

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Arbor Pharmaceuticals, LLC
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

ATTENTION: Allison Lowry
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated and received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triptorelin for Injectable Suspension, 22.5 mg.

We also refer to your correspondence, dated and received August 30, 2016, requesting review of your proposed proprietary name, Triptodur.

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

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Jennifer Johnson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/21/2016

From:	Johnson, Jennifer
To:	Allison Lowry (Allison.Lowry@ArborPharma.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (Triptodur): Clinical Information Request
Date:	Wednesday, November 16, 2016 5:25:00 PM
Attachments:	Financial Certification and Disclosure.pdf

Hello Allison,

Regarding your NDA 208956, Triptodur (triptorelin), we see that you have included the required Financial Disclosure form 3455 (attached) and have marked box (2). However, a list of clinical investigators was not attached to the form. We also need a list of investigators who have conflicts of interest (if any), and the nature of the conflict(s) of interest for those investigators. Could you please submit that information as an amendment to the NDA?

Let me know if you have any questions. Thanks in advance.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Steven Caras, M.D.	Vice President, Clinical Development
FIRM/ORGANIZATION Arbor Pharmaceuticals, LLC	
SIGNATURE Steven Caras	DATE *(mm/dd/yyyy)* 05-05-2016

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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/s/

JENNIFER L JOHNSON
11/16/2016
Clinical IR from clinical reviewer Shannon Sullivan

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208956

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
Director, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated and received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Triptodur (triptorelin for (b) (4) suspension), 22.5 mg.

We also refer to your amendments dated August 30, and September 2 and 27, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **June 29, 2017**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 1, 2017.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

Please provide the percentage of children with luteinizing hormone (LH) suppression to pre-pubertal levels within subgroups by gender, race and ethnicity, or indicate where in the application this information can be found.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

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

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
11/13/2016

From: Lalmansingh, Anika
To: "allison.lowry@arborpharma.com"
Subject: NDA 208956- Information Request, 9/14/2016
Date: Wednesday, September 14, 2016 1:32:00 PM
Attachments: image013.png

Information Request – CMC only

NDA 208956

Good Afternoon Ms. Lowry,

We request submission of the following information by **September 27, 2016**:

Regarding the use of the following facilities, the FEI number for (b) (4) listed on the 356h form (dated 8/29/2016) are not valid. Our records indicate the valid (b) (4) and we did not find an entry in our databases for (b) (4). Provide an updated Form FDA-356h with corrected information for the following facilities:

(b) (4)

Kindly acknowledge receipt of this email.

Kind Regards.

-Anika
Anika Lalmansingh, PhD
Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356
anika.lalmansingh@fda.hhs.gov

Anika Lalmansingh

Digitally signed by Anika Lalmansingh
Date: 9/14/2016 01:35:59PM
GUID: 55370d2000cfd6978682b28ff465c2a6

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208956

NDA ACKNOWLEDGMENT

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
Director, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Triptodur (triptorelin for (b) (4) suspension), 22.5 mg

Date of Application: August 29, 2016

Date of Receipt: August 29, 2016

Our Reference Number: NDA 208956

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **October 28, 2016**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER L JOHNSON
09/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208956

PROPRIETARY NAME ACKNOWLEDGEMENT

Arbor Pharmaceuticals, LLC
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

ATTENTION: Allison Lowry
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated and received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triptorelin Pamoate for Injection, 22.5 mg.

We acknowledge receipt of your correspondence, dated and received August 30, 2016, requesting a review of your proposed proprietary name, Triptodur.

If the application is filed, the user fee goal date will be November 28, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Jennifer Johnson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Deveonne Hamilton-Stokes, RN, BSN, MA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DEVEONNE G HAMILTON-STOKES
09/09/2016

From:	Johnson, Jennifer
To:	"alowry@arborpharma.com"
Bcc:	Johnson, Jennifer
Subject:	NDA 208956 (triptorelin pamoate for (b) (4) suspension): Information Request
Date:	Tuesday, August 30, 2016 4:31:00 PM

Dear Allison,

We have received your new NDA 208956 (triptorelin pamoate for (b) (4) suspension) and have the following information request:

In the Clinical Summary of Module 2 of the NDA, you state that your drug product (triptorelin for injectable suspension) is the same the product approved under NDA 22437 (letter of cross-reference to NDA 22437 is provided in Module 1.4.2).
In the Quality Overall Summary of Module 2 as well as in the Quality Module 3, you reference Drug Master File (DMF) (b) (4) for all CMC information on the drug product (letter of authorization to reference DMF (b) (4) is provided in Module 1.4.1).

- **Provide a letter of cross-reference to NDA 22437 to reflect the name and address of the current applicant of NDA 22437, Allergan Sales, LLC.**
- **Clarify why both NDA 22437 and DMF (b) (4) are referenced for the CMC information on the drug product.**
- **Clarify whether the CMC information in DMF (b) (4) is identical to the currently approved information on the drug product (triptorelin for injectable suspension) in NDA 22437. If there is any difference in the information, provide a tabulated explanation of the differences.**
- **Provide the qualitative and quantitative composition (i.e., quantity per dose and quantity per vial) of the drug product batches used in the pivotal clinical studies.**

We respectfully request a response by close of business on Friday, September 2nd.
Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
08/30/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111504

MEETING MINUTES

J. Kay Noel and Associates
U.S. Agent for Debiopharm International SA
Attention: J. Kay Noel, Ph.D.
8371 Terrace Drive
El Cerrito, CA 94530

Dear Dr. Noel:

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

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2015. The purpose of the meeting was to discuss the clinical efficacy and safety information to support a New Drug Application (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, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, December 3, 2015; 12:00-1:00 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, MD 20903

Application Number: IND 111504
Product Name: triptorelin for (b) (4) suspension
Indication: treatment of children with central precocious puberty (CPP)
Sponsor Name: Debiopharm International SA

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Division Director
Marina Zemskova, M.D.	Clinical Team Leader
Smita Abraham, M.D.	Clinical Reviewer
Ronald Wange, Ph.D.	Nonclinical Team Leader
Federica Basso, Ph.D.	Nonclinical Reviewer
Pamela Lucarelli	Chief, Project Management Staff
Jennifer Johnson	Regulatory Project Manager

Office of Pharmaceutical Quality, Office of New Drug Products

Suong Tran, Ph.D.	Quality/CMC Lead

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader (Acting)
Ritesh Jain, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

Mark Rothmann, Ph.D.	Statistical Team Leader
Jiwei He, Ph.D.	Biometrics Reviewer

Office of Scientific Investigations, Division of Clinical Compliance Evaluation

Cynthia Kleppinger, M.D. Reviewer

Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Risk Management
Naomi Redd Reviewer

SPONSOR ATTENDEES
Representing Debiopharm International SA

Eija Lundström, M.D.	Medical Director
Annick Ménétrey, Ph.D.	Senior Scientific Officer
Valérie Nicolas	Senior Associate Director
Pierre Gorsgurin, MSc.	Director, Biostatistics & Data Management
Jean-Marc Serrano, Ph.D.	Senior Regulatory Affairs Manager
Peggy Lipp, MSc.	Director, Regulatory Affairs, Market Access & Business Intelligence
Ngoc-Phan Gabioud, Ph.D.	Regulatory Affairs Manager, Debiopharm Research and Manufacturing SA
Céline Anselmetti Dayer	Associate Director, Regulatory Affairs, Debiopharm Research and Manufacturing SA
Kay Noel, Ph.D.	U.S. Agent

Representing Arbor Pharmaceuticals

Allison Lowry	Director, Regulatory Affairs
Mary Lou Freathy	Vice President, Regulatory Affairs, Quality, Manufacturing
Steven Caras	Vice President, Clinical Affairs

1.0 BACKGROUND

The sponsor, Debiopharm International SA, is developing triptorelin for (b) (4) suspension 22.5 mg, for the treatment of children with central precocious puberty (CPP), to be administered every 24 weeks (168 days). This product, marketed as Trelstar 6-Month by Actavis Laboratories UT, is approved under NDA 022437 in the Division of Oncology Products 1 for the palliative treatment of advanced prostate cancer. Other products, also gonadotropin releasing hormone (GnRH) agonists, currently approved for treatment of CPP include the following: Lupron Depot-Ped (leuprolide acetate for depot suspension), Supprelin LA (histrelin acetate) subcutaneous implant and Synarel (nafarelin acetate) nasal spray.

The sponsor submitted a Pre-IND meeting request on February 18, 2011, and the meeting was denied on March 15, 2011. A new IND was submitted on May 11, 2011. A clinical Special Protocol Assessment (SPA) request was submitted on June 17, 2011, and a SPA-No Agreement letter issued on August 4, 2011. The SPA request was resubmitted on September 2, 2011, and a SPA-Agreement letter issued on October 21, 2011. Orphan drug designation was granted for this product and indication on August 20, 2012.

To support approval of the eventual NDA submission, the sponsor plans to submit results from Study 8206-CPP-301 entitled, "An open-label, non-comparative, multicenter study on efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in

patients suffering from central (gonadotropin dependent) precocious puberty (CPP)," submitted and agreed-upon under the SPA request submissions referenced above.

The sponsor submitted a Pre-NDA meeting request on September 17, 2015, and the meeting was granted on October 9, 2015. A meeting package was submitted on October 29, 2015.

FDA sent preliminary comments to the sponsor on November 30, 2015.

2.0 DISCUSSION

The sponsor's questions are repeated below in italicized text, followed by the FDA response (bolded) and meeting discussion (bolded/italicized).

Question 1: *In view of the FDA Special Protocol - Agreement and Debio 8206-CPP-301 study results:*

a) *Does FDA agree that the results of the Debio 8206-CPP-301 study are sufficient for filing an NDA in support of the 6-month triptorelin formulation for treatment of children with CPP?*
b) *Since Debiopharm proposes to provide a tabular summary of efficacy findings from published triptorelin CPP studies under Module 2.7.3 Summary of Clinical Efficacy, Section 2.7.3.3 Comparison and Analyses of Results Across Studies (see question 2), is it necessary to submit the NDA under section 505(b)(2) of the Food, Drug and Cosmetic Act?*

(b) (4)

FDA Response to Question 1a: **We agree that results of the Debio 8206-CPP-301 study support filing of your NDA for the 6-month triptorelin formulation for treatment of children with CPP.**

FDA Response to Question 1b: **If you own or have a right of reference to all of the data/information that you are relying upon for approval, then your application would be a 505(b)(1) application. Clarify whether you have the right of reference to the triptorelin NDA(s) and provide Letters of Authorization with your NDA submission.**

Please note, you can still submit literature in your 505(b)(1) application; the data from the literature will be considered supportive and will not replace the individual trial results when evaluating the evidence of efficacy and safety of your product for the treatment of children with CPP.

However, if any of the information that is essential for approval comes from studies not conducted by Debiopharm, and for which Debiopharm has not obtained a right of reference (for example, from published literature), then a 505 (b)(2) regulatory pathway will be appropriate for your intended application. We note that if you seek 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 these studies is scientifically appropriate.

Refer to the 505(b)(2) REGULATORY PATHWAY subsection under Section 3.0, OTHER IMPORTANT INFORMATION, at the end of this document for additional information regarding 505(b)(2) applications.

Additional Comments:

- **The draft labeling provided in Appendix E of the submitted briefing package includes safety and pharmacokinetic data from the published literature. However, the "data to support discussion" in Question 9 of the submitted briefing package (page 24) indicates that you will only use safety data from the pivotal Debio 8206-CPP-301 to inform the label. Clarify this discrepancy.**

- **Indicate whether the pediatric pharmacokinetic and pharmacodynamic labeling information will be derived only from Debio 8206-CPP-301 study results or if you plan to rely on published literature. If you plan to rely on literature or other studies for which you have no right of reference but that are necessary for approval, please refer to our response to Question 1b regarding the 505(b)(2) regulatory pathway.**

- **Clarify if the triptorelin formulation used in the Debio 8206-CPP-301 study is the same as the to-be-marketed formulation for the treatment of children with CPP. Refer to the response to Question 7.**

Discussion during FDA meeting: ***The sponsor clarified that they plan to file the NDA via the 505(b)(1) regulatory pathway, and that the literature submitted with the application will be supportive only. The sponsor also confirmed that the triptorelin formulation used in the 8206-CPP-301 study is the same as the to-be-marketed formulation for the treatment of children with CPP.***

The sponsor requested clarification as to what safety data FDA expects to be included in the labeling. The sponsor also asked whether pharmacovigilance data for the CPP patient population, as well as information on the expected class effects for GnRH agonists should be included in the label. FDA clarified that if the sponsor believes that safety issues apply to the product class, they can include safety information derived from pharmacovigilance data pertinent to this class (including use of the specific product in Europe). FDA will review all safety information, including information related to class effects proposed to be labeled. FDA stated that the sponsor should provide a clear rationale for inclusion of supportive safety data in the label. The

rationale should emphasize the relevance of the safety information to the proposed indication and to the specific product. For example, some of the safety information on use in the prostate cancer population may not be relevant to use in the CPP population.

(b) (4)

Question 2: *Does FDA agree that the Clinical Study Report for the Debio 8206-CPP-301 study may serve as the Integrated Summary of Efficacy and the Integrated Summary of Safety for the CPP NDA?*

FDA Response to Question 2: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 3: *In the event of an update of the referenced SDRG/ADRG standards prior to submission of the CPP NDA, would the FDA accept a CPP NDA submission that uses the SDRG/ADRG standards in effect at the time of the pre-NDA meeting?*

FDA Response to Question 3: **Yes, it is acceptable as long as the SDRG/ADRG describe any special considerations or directions that may facilitate FDA reviewers' use of the submitted data and help reviewers understand the relationships between the study report and data. Please refer to *Study Data Technical Conformance Guide* pg 4-5.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 4:

a) *Does FDA agree that the pharmacokinetic and pharmacodynamic assessments agreed in the Special Protocol Assessment are sufficient to support NDA filing?*
b) *For the CPP labeling, does FDA agree that it is sufficient to include only those pharmacokinetic and pharmacodynamics assessments performed in children with CPP?*

FDA Response to Question 4a: **Yes, we agree that the pharmacokinetic and pharmacodynamic assessments as agreed upon in the Special Protocol Assessment are sufficient to support NDA filing.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

FDA Response to Question 4b: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 5: *Does FDA agree that it is not necessary to include an assessment of abuse potential in the CPP NDA?*

FDA Response to Question 5: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 6:

a) *Does FDA agree that for the CPP NDA, since information on nonclinical studies will be incorporated by cross-reference to the approved triptorelin NDAs, under an appropriate Letter of Authorization, Module 2.6 Nonclinical Written and Tabulated Summaries and Module 4 Nonclinical Study Reports will not be included in the CPP NDA?*
b) *Does FDA agree that for the CPP NDA, results for the in vitro pharmacokinetic drug interaction studies may be included in Module 2.7.2 Summary of Clinical Pharmacology Studies, Section 2.7.2.2.1 In Vitro Drug-Drug Interaction Studies, with study reports included in Module 5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials, Section 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies?*

FDA Response to Question 6a: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

FDA Response to Question 6b: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 7:

a) *Since Triptorelin for* (b) (4) *Suspension 22.5 mg manufactured by Debiopharm has been approved for marketing for treatment of men with advanced prostate cancer under NDA 022437 and the CPP NDA will cross-reference the approved NDA 022437, under an appropriate Letter of Authorization,* (b) (4)

(b) (4)

c) *Since the CPP NDA will cross-reference both Debiopharm's new Type II DMF for Drug Product (triptorelin pamoate microgranules in unlabeled vials) and the approved NDA 022437, under appropriate Letters of Authorization, does FDA agree that Module 2.3 will include only drug substance specifications, drug product specifications, drug product composition, and differences in CMC information between the two cross-references?*

(b) (4)

information for triptorelin 1-month (3.75 mg), 3-month (11.25 mg), and 6-month (22.5 mg) sustained release formulations?

f) *Once Debiopharm's Type II DMF for Triptorelin Drug Product is accepted during review of the CPP NDA, is it acceptable for FDA to cross-reference the Type II DMF to the already approved triptorelin NDAs, to facilitate FDA review of post-approval changes?*

FDA General Comment Regarding Question 7: **As detailed in FDA Guidance Document "Drug Master Files: Guidelines" (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm) section IV. C.1.b(2), manufacturing and controls information for finished dosage forms should ordinarily be submitted in an IND or NDA rather than in a DMF. If this information cannot be submitted in the NDA, it could be submitted in a DMF. Since it appears that in the situation you have described, the CMC information could be submitted in the NDAs, the use of a DMF does not appear to be warranted.**

FDA Response to Question 7a: **No, we do not agree to your proposal.** (b) (4)

(b) (4)

FDA Response to Question 7b: **See our General Comment Regarding Question 7. No, we do not agree with your proposal.** (b) (4)

(b) (4)

[redacted]

FDA Response to Question 7c: **See our General Comment Regarding Question 7. If the submission of the drug product DMF is necessary, we agree to your proposed Module 2.3 provided that you submit the information in Module 3 as discussed in the response to Question 7a.**

FDA Response to Question 7d: **No, we do not agree to your proposal.** (b) (4)

(b) (4)

[redacted]

FDA Response to Question 7e: **See our General Comment Regarding Question 7. If the submission of the drug product DMF is necessary, we agree that CMC information on different dosage strengths can be included in one DMF.**

FDA Response to Question 7f: **See our General Comment Regarding Question 7. Your question is unclear. For post-approval changes, the NDA applicant reports the change in a supplement or in the annual report, depending on the category of the change. You can authorize the NDA applicant to reference information in your DMF in support of the change, and this authorization should be included in the supplement or annual report as part of the documentation supporting the change.**

Changes in the CMC information for the approved triptorelin NDAs should be reported in accordance with 21 CFR 314.70. You can authorize the applicants of these NDAs to reference information in your DMF in support of the specific change, and this authorization should be included in the supplement or annual report as part of the documentation supporting the change. We reiterate part of our response to question 7b: Since the new NDA will cross-reference the approved NDA 022437, FDA approval of the changes in the CMC information for NDA 022437 requiring FDA approval should precede the inclusion of the information in your new NDA.

Discussion during FDA meeting: ***The sponsor stated that submission of a DMF (rather than just cross-referencing the approved prostate cancer NDA 022437) would be necessary and wanted to know if FDA was recommending against the sponsor's plan to submit one. FDA replied that, as stated in the preliminary response to this question, the***

sponsor may submit a DMF but that submitting all information in the NDA is preferred. The sponsor said that the current applicant for NDA 022437 has submitted a prior approval manufacturing supplement (PAS) that has not yet been approved (action goal date in April 2016) and wanted to know if the information regarding this change should be submitted in the DMF. FDA confirmed the preliminary response to this question, that all CMC information has to be identical in both the referenced NDA and the DMF and that any new CMC information should be included in both. The sponsor said that they anticipate submitting the new NDA prior to approval of the PAS, and wanted to know if the PAS submission information should be included in the DMF. Again, FDA confirmed the preliminary response to this question, that any manufacturing changes in the referenced NDA should be approved prior to submission of a new NDA, in order to avoid the scenario in which an NDA is submitted without all of the required new information and then amending it later during the NDA review cycle or the scenario in which the new information is submitted to the new NDA and DMF and then the PAS is not approved. The sponsor further explained that in order to prepare for a first quarter 2016 NDA submission, the DMF must be submitted to FDA by the end of January. FDA reminded the sponsor that an NDA must be complete at the time of submission. The sponsor will be taking a risk by submitting the NDA prior to approval of the new CMC information. If the sponsor opts to submit new CMC information to the NDA during the review cycle (once the PAS is approved), FDA could designate the submission containing the new information as a major amendment which would extend the review clock.

The sponsor asked if they need to submit both a summary module and Module 3 since they will be cross-referencing approved NDA 022437. FDA referred the sponsor to the preliminary response to Question 7a for the information to be included in Module 3 of the new NDA. The sponsor argued that the NDA will also be missing Module 4 and wanted to know why they need to submit Module 3. FDA replied that Module 3 needs to contain all pertinent up-to-date manufacturers' information so that inspections can be planned as well as basic information needed for the labeling review. The requested limited information should be included in the new NDA because the NDA applicant is ultimately responsible for 100% of the CMC information, even if most of the information is in a DMF.

Post-meeting additional comment: ***Letters of authorization for the reference of other NDAs and DMFs will be included in Module 1, along with the Environmental Analysis statement specific for the new NDA. Also, a complete list of all testing and manufacturing facilities used for the commercial drug substance and drug product will be included on the Form 356h of the new NDA as well as in Module 3, with contact information and a statement that all facilities will be ready for the GMP inspection at the time of the NDA submission. The information will include all manufacturing, testing, and packaging facilities listed in any Type II DMF supporting the new NDA.***

Question 8:

a) Does FDA agree with the proposed format and content of the CPP NDA?

b) *Does FDA agree that it will not be necessary to include information and study reports that have been cross-referenced to the approved triptorelin NDAs, under appropriate Letters of Authorization?*

FDA Response to Question 8a: **Yes, the proposed format and content for the CPP NDA seems acceptable.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

FDA Response to Question 8b: **Yes, we agree.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 9: *Does FDA agree that the proposed draft labeling is a suitable template for labeling to be included in the CPP NDA?*

FDA Response to Question 9: **We remind you that your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm) and PLLR Requirements for Prescribing Information (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm) websites.**

The content of the triptorelin label for the CPP indication will reflect the specific information contained in the application. We cannot comment at this time about any labeling claim or formatting without a review of the NDA data.

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 10: *Does FDA agree that a REMS will not be required for the CPP NDA?*

FDA Response to Question 10: **At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of triptorelin outweigh the risks, and if it is necessary, what the required elements will be. The NDA submission does not need to include a REMS proposal. However, we remind you that the need for a REMS will be determined during the review of the application.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 11: *Does FDA agree that it will not be necessary to include a Pediatric Study Plan in the CPP NDA?*

FDA Response to Question 11: **Yes. Please note that being an orphan drug application, your NDA is exempted from the requirements of the Pediatric Research and Equity Act.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

Question 12: *Does FDA agree that the CPP NDA will be exempt from the requirement to pay an application fee or product fees?*

FDA Response to Question 12: **Orphan drug applications are exempt from paying user fees; however, any questions should be directed to the User Fee Staff at CDER-PDUFA@fda.hhs.gov or by phone: 301-796-7900.**

Discussion during FDA meeting: ***The sponsor told FDA that the orphan drug grant would be transferred to Arbor Pharmaceuticals, and asked if transfer and acceptance letters should be submitted to the NDA to verify that this had been done; FDA agreed.***

Question 13: *Does FDA agree that the CPP NDA will qualify for Priority Review Designation?*

FDA Response to Question 13: **The decision as to whether your application will receive a "priority" or "standard" review classification will be made at the filing meeting. You will be notified of a priority review designation by post-submission day 60 or by post-submission day 74 in the case of a standard review designation.**

Discussion during FDA meeting: ***None, sponsor accepts FDA response.***

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, 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, in part, 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	
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.

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical

investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which Sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

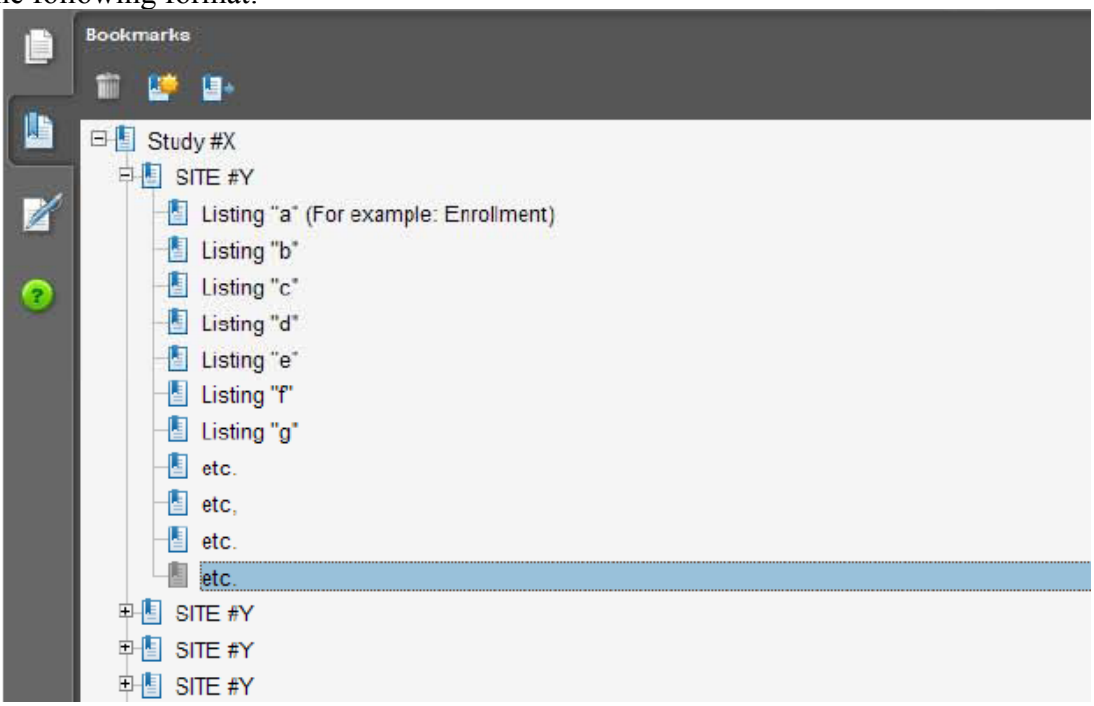
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates

g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Discussion during FDA meeting: ***The sponsor agreed to comply with required OSI requests I (request for general study related information and comprehensive clinical investigator***

information) and II (request for subject level data listings by site) but requested exemption for request III (site level dataset) since they only have one small clinical study. FDA agreed, and reminded the sponsor to be sure that everything needed for inspection is available at the clinical site (i.e., if data results are generated at a central laboratory, the sponsor should ensure that these are sent to the clinical site once the trial has completed).

Attachment 1

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

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

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items that were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

JEAN-MARC P GUETTIER
12/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111504

SPECIAL PROTOCOL - AGREEMENT

J. Kay Noel and Associates
U.S. Agent for Debiopharm SA
Attention: J. Kay Noel, Ph.D.
8371 Terrace Drive
El Cerrito, CA 94530

Dear Dr. Noel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Triptorelin for (b) (4) Suspension, 22.5 mg.

We acknowledge your request dated September 2, 2011, received on September 6, 2011, for a special protocol assessment of a clinical protocol. The protocol Debio 8206-CPP-301 (Study 301) is titled "An open-label, non-comparative, multicenter study on efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin dependent) precocious puberty (CPP)".

We note that this protocol includes revisions discussed in our August 4, 2011, "Special Protocol Assessment – No Agreement" letter.

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see "Guidance for Industry: Special Protocol Assessment").

We also have the following responses to your questions.

1. Does the Agency agree that the design of the study proposed is appropriate?

FDA Response: The design of the study is acceptable; we recognize your intention to market only the 6-month triptorelin formulation for the central precocious puberty indication. (b) (4)

(b) (4)

From a statistical perspective, the revised protocol has addressed the concerns that we expressed in response to the previous submission. Specifically: (1) the revised protocol uses the definition of the intention-to-treat (ITT) analysis population that we recommended, including only subjects who have been enrolled, treated at baseline, and who have at least one post treatment assessment of luteinizing hormone (LH) suppression status; (2) In the ITT population, subjects who discontinue from the study prior to the month six assessment for any reason or who otherwise do not provide an assessment of LH suppression at month 6 will be classified as "not suppressed" with respect to the primary endpoint; (3) For the primary and secondary endpoints that involve LH, the primary analyses of the LH endpoints will reference the modified ITT (mITT) population. Supportive analyses will reference the Per Protocol population. (4) For the secondary LH endpoint "maintenance of LH suppression from Month 3 through Month 6": the revised protocol includes a reasonable plan for classifying the status of subjects who withdraw or otherwise do not provide LH data at intermediate or endpoint visits.

2. Does the Agency agree with the proposed eligibility criteria?

FDA Response: The eligibility criteria are acceptable.

3. Does the Agency agree with the proposed primary endpoint of percentage of patients achieving LH suppression to prepubertal levels at Month 6 (Day 169)?

FDA Response: The proposed primary endpoint is acceptable. The revised protocol incorporates the recommendations we made concerning the primary endpoint and the primary analysis population. These are summarized in response to Question 1. In addition, the revised protocol includes modifications to the statistical analysis that take into account the extension of the overall study duration from 6 to 12 months and the additional LH suppression limit of 4 IU/L. (We note that the primary endpoint will still be assessed at month 6.)

4. Does the Agency agree with the definition of LH suppression to prepubertal levels as serum LH ≤ 5 IU/L 30 minutes after GnRH agonist stimulation [leuprolide acetate 20 mcg/kg SC]?

FDA Response: The proposed definition is acceptable. In addition, the revised protocol includes a secondary analysis based on LH suppression of ≤4 IU/L 30 minutes after GnRH agonist stimulation.

5. Does the Agency agree with the proposed secondary hormonal and clinical efficacy endpoints and their time points?

FDA Response: The proposed secondary endpoints and their time points are acceptable. The revised protocol has added descriptive statistics by timepoint for GnRH-stimulated LH levels, basal estradiol (in females) and testosterone (in males), including change from baseline.

6. Does the Agency agree that it will be sufficient to assess serum triptorelin levels in all patients at Months 1, 2, 3, 6, 9, and 12 and to assess triptorelin C_{max} (and t_{max}) in a subset of eight (8) patients following the first and second injections?

FDA Response: **Yes, your plan seems reasonable.**

7. Does the Agency agree with the proposed safety assessments?

FDA Response: **The proposed safety assessments are acceptable.**

8a. Does the Agency agree with the proposed sample size?

FDA Response: **The revised protocol incorporates the recommendations we made concerning the number of subjects to be enrolled in Study 301. You have re-calculated the study size based on a one-tailed α of 0.025, an alternative percentage suppression of 95%, a null percentage of suppression of 80%, and a 5% dropout rate prior to any post-clinic visits. The proposed number of 44 patients to be enrolled incorporates these recommendations.**

8b. Does the Agency agree that the hypotheses of a true proportion of 95% and a null proportion of 80% of patients achieving prepubertal serum levels of stimulated LH at Month 6 will support NDA filing?

FDA Response: **The null percentage of 80% may suggest a criterion level for the lower confidence bound of the estimate of percentage suppression at month 6. While this lower bound (of the two-sided 95% CI) may give helpful guidance about the efficacy of this product, we note that the evaluation of efficacy will be a review issue.**

9. Does the Agency agree that that the proposed single multicenter, single-arm, open-label, non-comparative registrational study of the triptorelin 6-month formulation, (b) (4) for treatment of CPP, will be sufficient to support NDA filing?

FDA Response: **The proposed study with the added modifications provided in the responses above appear sufficient for filing an NDA in support of the 6-month triptorelin formulation assuming that all other conditions necessary for filing an application are met. Please note that if you intend to submit published literature data in support of your application you will have to submit the NDA under section 505(b)(2) of the Food, Drug and Cosmetic Act. We advise you to re-visit this issue at the pre-NDA meeting.**

10. Does the Agency agree that the study will include at least four (4) boys?

FDA Response: **Yes, this is acceptable.**

11. Does the Agency agree that the recent approval of sustained-release formulations of another GnRH agonist analog for treatment of CPP will not preclude approval of Triptorelin for (b) (4)

Suspension 22.5 mg for treatment of CPP, assuming sufficient evidence of efficacy and safety is generated in the proposed study under SPA agreement?

FDA Response: As with any application, your submission is judged on its own merit.

In addition, we have the following comments.

12. Profile plots: Your revised protocol incorporates the use of individual patient profile plots depicting the time course of LH and either estradiol or testosterone for each patient. The description of these profile plots incorporates the recommendations we made in response to the original SPA submission.

13. Data standards: The revised protocol does not describe the use of data standards. We continue to recommend the implementation and use of data standards for the submission of applications for product registration. The Center for Drug Evaluation and Research (CDER) has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. The web page may be found at the following link:

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

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this new clinical protocol. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking

regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 11504**, clinical protocol submitted on September 2, 2011, your clinical protocol number, if available, and that it contains the FDA Form 3674 that was to accompany that submission.

If you have already submitted the certification for this submission, please disregard the above.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
10/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111504

**SPECIAL PROTOCOL ASSESSMENT -
NO AGREEMENT**

J. Kay Noel and Associates
U.S. Agent for Debiopharm SA
Attention: J. Kay Noel, Ph.D.
8371 Terrace Drive
El Cerrito, CA 94530

Dear Dr. Noel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Triptorelin for (b) (4) Suspension, 22.5 mg.

We acknowledge your request dated June 17, 2011, received on June 20, 2011, for a special protocol assessment of a clinical protocol. The protocol is titled "An open-label, non-comparative, multicenter study on the efficacy, safety and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty (CPP)".

We have completed our review and, based on the information submitted, have determined that that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission.

We also have the following responses to your questions.

1. Does the Division agree that the design of the study proposed is appropriate?

   FDA Response:

   While the proposed treatment duration of 24 weeks (6 months) is sufficiently long to assess the effect of a single triptorelin injection on the primary and secondary hormonal and clinical endpoints, it provides no information regarding continued safety and efficacy beyond the initial single dose. Therefore, the duration of this Phase 3 study should be extended to 12 months in order to assess the durability of triptorelin's effect on efficacy as well as a favorable safety profile beyond 6 months including the demonstration of lack of an "acute over chronic" effect at the time of repeat dosing.

(b) (4)

(b) (4)

We recommend that the definition of the intention-to-treat analysis population be modified to include only subjects who have been enrolled, treated at baseline, and who have at least one post-treatment assessment of LH suppression status.

For the modified ITT (mITT) population, we also recommend that subjects who discontinue from the study prior to the month six assessment for any reason or who otherwise do not provide an assessment of LH suppression at month 6 be classified as "not suppressed" with respect to the primary endpoint.

For the primary and secondary endpoints that involve LH, we recommend that the primary analyses of the LH endpoints reference the mITT population. Supportive analyses can reference the Per Protocol population.

For the secondary LH endpoint "maintenance of LH suppression from Month 3 through Month 6", we note that you made a distinction between discontinuation for drug-related reasons and discontinuation for non-drug-related reasons. However, in clinical studies this distinction is not always clear for each subject who withdraws or otherwise does not provide an assessment at a pre-specified clinic visit. For this reason we recommend classifying subjects who withdraw for any reason or who otherwise do not provide LH data at Month 3 or Month 6 as "not suppressed" with respect to the maintenance endpoint.

2. Does the Agency agree with the proposed eligibility criteria?

FDA Response:

Yes.

3. Does the Agency agree with the proposed primary endpoint of percentage of patients achieving LH suppression to pre-pubertal levels at Month 6 (Day 169)?

FDA Response:

The recommendations concerning the primary endpoint and the primary analysis population in response to Question 1 will affect the calculation of the proposed primary LH endpoint.

4. Does the Agency agree with the definition of LH suppression to pre-pubertal levels as serum LH ≤5 IU/L 30 minutes after GnRH agonist stimulation (leuprolide acetate 20 mcg/kg SC)?

FDA Response:

Yes; however, we also request that you perform a secondary analysis based on LH suppression of ≤ 4 IU/L 30 minutes after GnRH agonist stimulation.

5. Does the Agency agree with the proposed secondary hormonal and clinical efficacy endpoints and their time points?

FDA Response:

In addition to the proposed secondary efficacy endpoints, provide descriptive statistics by timepoint for GnRH-stimulated LH levels, basal estradiol (in females) and testosterone (in males), including change from baseline.

For PK sampling, please refer to Question 6.

6. Does the Agency agree that it will be sufficient to assess the serum triptorelin levels at Months 1, 2, 3 and 6 and that more frequent PK samplings for establishing of a complete PK profile will be unnecessary?

FDA Response:

No. In addition to your proposed PK sampling in all subjects at months 1, 2, 3, and 6, we recommend you to characterize the Cmax from the formulations studied. Cmax can be characterized in a subset of subjects. In addition, if the Phase 3 study is conducted for 12 months, we strongly encourage you to assess serum triptorelin levels following multiple doses.

7. Does the Agency agree with the proposed safety assessments?

FDA Response:

The proposed safety assessments are acceptable.

8a. Does the Agency agree with the proposed sample size?

FDA Response:

Please see our response to Question 1. Your sample size will need to be recalculated if a second treatment arm is to be evaluated.

Regarding your current proposal, the proposed sample size of 46 patients is acceptable. We note that this study size refers to the mITT population. For this reason, you may want to increase the number of subjects enrolled in the study by a small percentage to allow for dropouts prior to any post-clinic visits.

With regard to the statistical calculations, you have calculated the study size based on a one-tailed α of 0.05. However, we will require a one-tailed α of 0.025. You have also proposed a percentage of suppression of 97.5% for the alternative hypothesis. However, because of our recommendations for the mITT analysis population, this percentage may be closer to 95%. The null percentage of suppression of 85% can be changed to 82.5% or 80%.

8b. Does the Agency agree that the hypotheses of a true proportion of 97.5% and of a null proportion of 85% of patients achieving pre-pubertal serum levels of stimulated LH at Month 6 will support NDA filing?

FDA Response:

We suggest a somewhat lower true percentage of 95% and null percentage of 82.5% or 80%, considering our recommended modification to the ITT population as described in our responses to Question 1 and 8a. In addition, we note that the null percentage may suggest a criterion level for the lower 95% confidence bound to the estimate of percentage suppression from the study results. While this lower bound may give helpful guidance about the efficacy of this product, we note that the evaluation of efficacy will be a review issue.

9. Does the Agency agree that the study will include at least 4 boys (8.7% of patients)?

FDA Response:

We agree with the approximate percentage of boys enrolled. The actual number will need to be adjusted if two dosing regimens are evaluated.

FDA Response:

(b) (4)

In addition, we have the following comments.

1. **Profile plots: We request that you provide individual patient profile plots that depict the time course of LH and either estradiol or testosterone for each patient from baseline to month 6. We request one page for each subject. On each page, provide two plots: (1) a profile plot of LH and (2) a profile plot of estrogen or testosterone, from baseline to month 6.**

   A. Annotate each subject's plot with the following information:
      a. Subject information: ID, sex, race, age at start of treatment, baseline BMI SD score (≤ median, > median), time between onset of puberty and start of treatment (≤ median, > median), age at onset of puberty (≤ median, > median), predicted adult stature compared to lower bound of range of target height.
      b. Disposition status (completed, discontinued, reason for discontinuation).
      c. Status with respect to membership in the intention-to-treat analysis database.
      d. Status with respect to primary efficacy endpoint.

   B. For LH, estradiol and testosterone profiles: Create the profile plot, with profile lines connecting symbols, for the LH levels. Use a horizontal line to depict the criterion level for suppression.

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

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

If you choose to revise this protocol and submit another request for special protocol assessment prior to study initiation, it should address all the issues itemized above and be prominently labeled as a "**Special Protocol Assessment – Resubmission.**" In addition, your cover letter should clearly reference the date and type of your original SPA submission as well as the following SPA reference number: 1. To facilitate review of your SPA resubmission, send a copy of the cover letter to Jennifer Johnson.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting and will be limited to the discussion of this protocol. For additional information, refer to FDA's "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm153222.pdf.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this new clinical protocol. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

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When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 111504**,

clinical protocol submitted on June 17, 2011, your clinical protocol number, if available, and that it contains the FDA Form 3674 that was to accompany that submission.

If you have already submitted the certification for this submission, please disregard the above.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
08/04/2011