

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206628Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206628

HFD # 170

Trade Name: Not Available

Generic Name: dexmedetomidine hydrochloride

Applicant Name: HQ Specialty Pharma Corporation

Approval Date, If Known: October 21, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

The submission contains only published literature to support the indication. The Applicant did not conduct any clinical studies to support the safety and efficacy of this product.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

No

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA 206628
NDA #(s).

NDA# 021038

Precedex (dexmedetomidine hydrochloride)

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2

YES

NO

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

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

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

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

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

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

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

Investigation #1 !

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YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

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

YES NO

If yes, explain:

=====
Name of person completing form: Allison Meyer
Title: Regulatory Health Project Manager
Date: October 20, 2015

Name of Office/Division Director signing form: Rigoberto Roca, Deputy Director
Title: Deputy Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ALLISON MEYER
10/21/2015

RIGOBERTO A ROCA
10/21/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206628 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Established/Proper Name: Dexmedetomidine Hydrochloride Dosage Form: Injection		Applicant: HQ Specialty Pharma Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 21, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None CR 3/12/15
❖ 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 _____		<input type="checkbox"/> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP 10/21/15, CR 3/12/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	n/a
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 2/6/15 DMEPA: <input type="checkbox"/> None 1/12/15, 2/5/15, 6/11/15 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 3/11/15, 8/21/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/19/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 3/11/15, 7/21/15
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>application did not trigger PREA</u> 	
❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	7/29/15, 7/13/15, 4/29/15, 3/5/15, 3/3/15, 2/24/15, 2/20/15, 2/19/15, 2/12/15, 2/5/12, 2/3/15, 1/26/15, 1/21/15, 1/13/15, 1/8/15 12/19/14, 11/19/14, 11/17/14, 9/9/14, 8/1/14, 7/24/14, 7/7/14, 6/24/14, 6/12/14, 5/20/14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	PIND 9/24/13
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/12/15, 10/21/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/12/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 10/21/15
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	2/5/15, 7/10/14
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	2/5/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/3/15, 6/27/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/6/15, 7/14/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/2/15
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/13/15, 3/11/15, 7/16/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 4/29/15, 3/9/15, 6/9/14
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 2/24/15, 6/29/15 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

ALLISON MEYER
10/26/2015

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, July 29, 2015 1:44 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628 package insert
Attachments: clean working copy FDA.doc

Please review the attached package insert labeling and let me know if you have any questions/comments.
Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
07/29/2015

Meyer, Allison

From: Meyer, Allison
Sent: Monday, July 13, 2015 9:44 AM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: PMR protocol

We acknowledge receiving a protocol for your screening leachables study in your submission dated 3/6/2015 and have the following comments. For your leachables assessment, evaluate three batches of your drug product over the course of your stability studies. We also remind you as part of your Post-marketing Requirement (PMR) that you must also submit a toxicological risk assessment that accompanies your leachables study report.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Monday, July 13, 2015 9:43 AM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628 PMR

Jeanne,
Please provide dates for the following PMR below. Please note there is a slight change in the language from last cycle.

PMR/PMC Description: Conduct an adequate leachable safety assessment for the (b) (4) [redacted] grey (b) (4) rubber stopper used in your container closure system. This assessment must include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
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/s/

ALLISON MEYER
07/13/2015



NDA 206628

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

HQ Specialty Pharma Corporation
120 Route 17 North
Paramus, NJ 07652

Attention: Joseph Pizza
President

Dear Mr. Pizza:

We acknowledge receipt on April 21, 2015, of your April 21, 2015, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dexmedetomidine Hydrochloride Injection, 400 mcg/4 mL and 1000 mcg/10 mL.

We consider this a complete, class 2 response to our March 12, 2015, action letter. Therefore, the user fee goal date is October 21, 2015.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ALLISON MEYER
04/29/2015

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, March 03, 2015 4:10 PM
To: 'Jeanne Squeglia'
Subject: RE: NDA 206628

Jeanne,

The data only submitted results from 4/5 microorganisms in the compendial test. We are missing the data from E. coli. You state that you used all compendial organisms but for some reason only provided data on 4/5.

Provide the E. Coli data by March 5th.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, March 05, 2015 11:25 AM
To: 'Jeanne Squeglia'
Subject: RE: NDA 206628

Jeanne,

With respect to your patent information: the applicant should again be requested to provide a calendar date to which they consent to FDA approval. This was not mentioned in your last submission. This information is needed by 3.9.15.

Allison

From: Meyer, Allison [Allison.Meyer@fda.hhs.gov]
Sent: Tuesday, February 24, 2015 12:34 PM
To: Jeanne Squeglia
Subject: NDA 206628

Jeanne,

Please confirm receipt of the following email information that was sent on 2/20. Also provide a date of intended response.

The patent certification for the 6,716,867 ('867) patent was changed to paragraph IV on 1/29/15 and notice was provided on 2/5/15 and 2/6/15 as required by regulation. Submit a letter to FDA from the patent owner stating that it has a licensing agreement with HQ Specialty Pharma and that the patent owner consents to full FDA approval; this letter should include the date upon which the patent owner consents to full FDA approval.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, February 24, 2015 12:34 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628

Jeanne,

Please confirm receipt of the following email information that was sent on 2/20. Also provide a date of intended response.

The patent certification for the 6,716,867 ('867) patent was changed to paragraph IV on 1/29/15 and notice was provided on 2/5/15 and 2/6/15 as required by regulation. Submit a letter to FDA from the **patent owner** stating that it has a licensing agreement with HQ Specialty Pharma and that the patent owner consents to full FDA approval; this letter should include the **date** upon which the patent owner consents to full FDA approval.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 19, 2015 3:10 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: package insert

Jeanne,

Which specific version or versions of which labels did you use to develop the latest package insert?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 12, 2015 6:34 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628 PMR

Jeanne,
Response to the following is due by 2/18/15:

PMR/PMC Description: Conduct an adequate leachable safety assessment for the (b) (4) [redacted] grey (b) (4) rubber stopper used in your container closure system. This assessment must include leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceed (b) (4) mcg/day.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
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/s/

ALLISON MEYER
03/10/2015

Meyer, Allison

From: Meyer, Allison
Sent: Friday, February 20, 2015 11:00 AM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628

Jeanne,

The patent certification for the 6,716,867 ('867) patent was changed to paragraph IV on 1/29/15 and notice was provided on 2/5/15 and 2/6/15 as required by regulation. Submit a letter to FDA from the patent owner stating that it has a licensing agreement with HQ Specialty Pharma and that the patent owner consents to full FDA approval; this letter should include the date upon which the patent owner consents to full FDA approval.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
02/20/2015

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 12, 2015 6:34 PM
To: 'Jeanne Squeglia'
Subject: RE: dexmedetomidine labeling IR

Jeanne,
Can you please expand on why you cannot revise the specifications for the microbial effectiveness study?

Allison

-----Original Message-----

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Thursday, February 12, 2015 10:33 AM
To: Meyer, Allison
Subject: RE: dexmedetomidine labeling IR

Thank you Allison

Can you please provide the Post Marketing Form referenced on the teleconference? In addition, we would like to discuss our possible options for the leachable study.

In regards to the microbial effectiveness study, we can not revise the specifications. However, we can commit to having the results to the Agency by week of March 2.

Can we set up another call to discuss these two issues?

Looking forward to your response,
Jeanne

From: Meyer, Allison [Allison.Meyer@fda.hhs.gov]
Sent: Tuesday, February 10, 2015 4:34 PM
To: Jeanne Squeglia
Subject: RE: dexmedetomidine labeling IR

Dr. Roca; Deputy Director
Dr. Woo; Pharm/Tox Reviewer
Dr. Cole; Microbiology Reviewer
Dr. Pinto; ONDQA Branch Chief
Dr. Lockett; Clinical Reviewer
And myself.

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Tuesday, February 10, 2015 4:42 PM
To: Meyer, Allison
Subject: Re: dexmedetomidine labeling IR

Allison

Please send attendee list.

Thank you,

Jeanne Squeglia

On Feb 9, 2015, at 12:27 PM, Meyer, Allison <Allison.Meyer@fda.hhs.gov<<mailto:Allison.Meyer@fda.hhs.gov>>> wrote: Jeanne,
I will email you the list after the teleconference. Yes, PMR refers to post-marketing requirements. I have the call in number. We will be calling you at 2:10 pm.

Thanks,
Allison

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Monday, February 09, 2015 10:43 AM
To: Meyer, Allison
Subject: Re: dexmedetomidine labeling IR

Allison

Please provide a list of attendees for the call. Please also confirm PMR refers to post market requirements.

Finally please confirm you are in receipt of the call in numbers.

Thank you,

Jeanne Squeglia

On Feb 5, 2015, at 1:50 PM, Meyer, Allison <Allison.Meyer@fda.hhs.gov<<mailto:Allison.Meyer@fda.hhs.gov>>> wrote: Jeanne,

The Division will need to have a brief tcon with you regarding microbiology and PMR issues. I have reserved 2/9/15 at 2:10 pm. Please confirm. I will provide the call in number.

Thank you,
Allison

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Thursday, February 05, 2015 12:54 PM
To: Meyer, Allison
Subject: Re: dexmedetomidine labeling IR

Allison

The April 2 date is not a typo.

Jeanne Squeglia

On Feb 5, 2015, at 12:39 PM, Meyer, Allison <Allison.Meyer@fda.hhs.gov<<mailto:Allison.Meyer@fda.hhs.gov>>> wrote: Jeanne,
The labeling is still under review. I do not have a specific date that a fully completed label will be ready yet.

In the January submission regarding microbiology, you proposed an April 2nd date for updated information. This date is after our action date of March 12, 2015. Was the April 2nd date a typo? If so, what is the expected date of submission.
Allison

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Thursday, February 05, 2015 11:55 AM
To: Meyer, Allison
Subject: Re: dexmedetomidine labeling IR

Dear Allison

Please note response was submitted today through the gateway.

Please advise when we can expect full review of labeling and components.

Thanks
Jeanne Squeglia

On Feb 3, 2015, at 4:25 PM, Meyer, Allison <Allison.Meyer@fda.hhs.gov<<mailto:Allison.Meyer@fda.hhs.gov>>> wrote:
Remove the (b) (4) statement from the carton panel.

Response is needed by 2/6/15.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
02/19/2015

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 05, 2015 11:24 AM
To: 'Jeanne Squeglia'
Subject: RE: Information Request: NDA 206-628

Jeanne,
Have all the outstanding microbiology information requests been submitted? If so, please provide me the date of submission of the amendment.

Thanks,
Allison

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Saturday, December 20, 2014 7:07 AM
To: Johnson-Nimo, Maya
Cc: Rivera, Luz E (CDER); Meyer, Allison
Subject: Re: Information Request: NDA 206-628

Maya

We confirm receipt of the email. Further we request response be submitted week of January 5 as our CMO is now closed for the holidays.

Thank you.

Jeanne Squeglia

On Dec 19, 2014, at 4:16 PM, Johnson-Nimo, Maya <Maya.Johnson-Nimo@fda.hhs.gov> wrote:

Good afternoon Ms. Jeanne Squeglia:

PDUFA Goal Date: 3/12/15

We have started the review of NDA 206-628 and request additional information to continue our evaluation.

We refer to your 15 December 2014 amendment and the response to question 1 from the 17 November 2014 microbiology information request. We note your inclusion of antimicrobial effectiveness data from a similar drug product, (b) (4) that contained (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. While these data were adequate for the (b) (4) product, the applicability to your proposed product, 0.1 mg/mL dexmedetomidine hydrochloride, is not clear. If the dexmedetomidine hydrochloride contributes to the overall antimicrobial effectiveness of the final drug product, then the data generated with the (b) (4) product may not be applicable to the 0.1 mg/mL product. Either provide data that demonstrates no antimicrobial effects are contributed by the dexmedetomidine hydrochloride or provide data that demonstrates that 0.1 mg/mL dexmedetomidine hydrochloride with the minimum preservative content, or below, meets the USP<51> requirements.

Please submit the information requested by email to me and Dr. Luz E. Rivera (Luz.E.Rivera@fda.hhs.gov) and officially submit to the application by **Friday, January 2, 2015**.

Please acknowledge and confirm receipt of this request.

Thank you,

Maya Johnson-Nimo
Lead Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
WO - BLDG 21, RM2672
Direct Phone: 301-796-5885
Blackberry: (b) (4)
E-mail: Maya.Johnson-Nimo@fda.hhs.gov

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/s/

ALLISON MEYER
02/05/2015

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, February 03, 2015 4:11 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: dexmedetomidine labeling IR

Remove the (b) (4) statement from the carton panel.

Response is needed by 2/6/15.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
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/s/

ALLISON MEYER
02/05/2015

Meyer, Allison

From: Meyer, Allison
Sent: Monday, January 26, 2015 4:05 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: Information Request for NDA 206628.
Attachments: Information Request.doc

Response to the attached request is due by 1/30/15.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
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Information request –

- A. You commit to test (b) (4) annually for the API. This commitment is not specific. Clarify that you have properly qualified the supplier and support such claim with data and details; On condition of the qualification of the supplier, clarify that you will conduct full batch analysis on at least (b) (4) annually if there is manufacturing activity, and for the remaining batches you will at a minimum conduct the identification test to ensure that the correct drug substance will be used.
- B. Update the SPL table with correct contents in the marked locations.

DEXMEDETOMIDINE HYDROCHLORIDE			
dexmedetomidine hydrochloride injection, solution, concentrate			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC 00000-000
Route of Administration	INTRAVENOUS	DEA Schedule	
Active Ingredient/Active Moiety			
	Ingredient Name	Basis of Strength	Strength
DEXMEDETOMIDINE HYDROCHLORIDE	(b) (4)	DEXMEDETOMIDINE HYDROCHLORIDE	100 ug in 1 mL
Inactive Ingredients			
	Ingredient Name	Strength	
METHYLPARABEN	(b) (4)		
PROPYLPARABEN	(b) (4)		
SODIUM CHLORIDE	(b) (4)		

Packaging		
#	Item Code	Package Description
1	NDC:00000-000-00	4 in 1 CARTON
1		(b) (4)

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/s/

ALLISON MEYER
02/05/2015

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, January 21, 2015 4:25 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: dexmedetomidine NDA

Dear Ms. Squeglia:

This is in reference to your NDA # 206628 for dexmedetomidine Injection. You submitted your application on May 12, 2014, with the following indication.

Dexmedetomidine Hydrochloride Injection is a relatively selective alpha²-adrenergic agonist indicated for: Sedation of non-intubated patients prior to and/or during surgical and other procedures.

Your amendment dated July 1, 2014, has the following revised indication.

Dexmedetomidine Hydrochloride Injection is a relatively selective alpha²-adrenergic agonist indicated for:

(b) (4)

- Sedation of non-intubated patients prior to and/or during surgical and other procedures. (1.2)

Please refer to the Guidance for Industry: *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>

Please note that an original application can be submitted with multiple indications for which a single User Fee is assessed. However, if you amend a pending application and add another indication, it should be submitted in a separate original application, and you have to pay a separate User Fee for that. Refer to Section A/Original Applications and Amendments for further information.

We would be happy to set up a teleconference with our User Fee staff to discuss this matter with you.

Regards,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
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/s/

ALLISON MEYER
01/21/2015

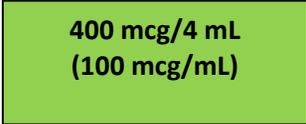
Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, January 13, 2015 2:01 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628 labeling recommendations

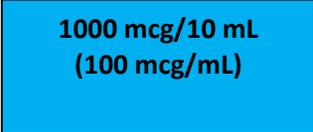
We recommend the following be implemented prior to action on this NDA:

A. CONTAINER LABELS AND CARTON LABELING

1. To help differentiate between the two product strengths (400 mcg/4 mL and 1,000 mcg/10 mL) and to mitigate product selection errors, incorporate a boxed background color for each strength. Ensure that the background colors are not similar in color to improve the differentiation between strengths, and ensure that the strength statement has adequate contrast with the background color. For example:



400 mcg/4 mL
(100 mcg/mL)



1000 mcg/10 mL
(100 mcg/mL)

B. Container Labels

1. Include the statement at the top of the principal display panel "4 mL Multi-Dose Vial" and "10 mL Multi-Dose Vial" to alert healthcare practitioners that the product is a multi-dose vial.
2. Increase the font size statement "Must be diluted" to increase the prominence of this important information.

C. Carton Labeling

1. Revise the statement (b) (4) on the 400 mcg/4 mL principle display panel to read "4 mL Multi-Dose Vial" to mitigate dosing errors. The statement should include the total volume of the solution (b) (4). We have identified post-marketing error cases where confusion has occurred around the total contents (b) (4) different from the total solution amount, has been used on the principal display panel.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
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/s/

ALLISON MEYER
01/16/2015

Rivera, Luz E (CDER)

From: Johnson-Nimo, Maya
Sent: Thursday, January 08, 2015 4:14 PM
To: Jeanne Squeglia
Cc: Rivera, Luz E (CDER); Cole, Jessica; Meyer, Allison
Subject: RE: Information Request: NDA 206-628

Follow Up Flag: Follow up
Flag Status: Completed

Thank you Jeanne!
We will be in contact with you soon.

Maya

From: Jeanne Squeglia [mailto:jsqueglia@hqspecialtypharma.com]
Sent: Thursday, January 08, 2015 4:24 PM
To: Johnson-Nimo, Maya
Cc: Rivera, Luz E (CDER)
Subject: Re: Information Request: NDA 206-628

Thank you Maya
Response submitted through gateway.

Jeanne Squeglia

On Jan 6, 2015, at 9:59 AM, Johnson-Nimo, Maya <Maya.Johnson-Nimo@fda.hhs.gov> wrote:

Good morning Ms. Squeglia: The response to the information request is due January 8th.

Thank you,
Maya

Maya Johnson-Nimo
Lead Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
WO - BLDG 21, RM2672
Direct Phone: 301-796-5885
Blackberry: (b) (4)
E-mail: Maya.Johnson-Nimo@fda.hhs.gov

From: Johnson-Nimo, Maya
Sent: Saturday, December 20, 2014 2:37 PM
To: 'jsqueglia@hqspecialtypharma.com'
Cc: Rivera, Luz E (CDER); Meyer, Allison
Subject: Re: Information Request: NDA 206-628

Jeanne - The date request change is approved, the revised submission date is Jan. 8th.

Thank you.

Maya Nimo

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Saturday, December 20, 2014 07:06 AM
To: Johnson-Nimo, Maya
Cc: Rivera, Luz E (CDER); Meyer, Allison
Subject: Re: Information Request: NDA 206-628

Maya

We confirm receipt of the email. Further we request response be submitted week of January 5 as our CMO is now closed for the holidays.

Thank you.

Jeanne Squeglia

On Dec 19, 2014, at 4:16 PM, Johnson-Nimo, Maya <Maya.Johnson-Nimo@fda.hhs.gov> wrote:

Good afternoon Ms. Jeanne Squeglia:

PDUFA Goal Date: 3/12/15

We have started the review of NDA 206-628 and request additional information to continue our evaluation.

We refer to your 15 December 2014 amendment and the response to question 1 from the 17 November 2014 microbiology information request. We note your inclusion of antimicrobial effectiveness data from a similar drug product, (b) (4) that contained (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. While these data were adequate for the (b) (4) product, the applicability to your proposed product, 0.1 mg/mL dexmedetomidine hydrochloride, is not clear. If the dexmedetomidine hydrochloride contributes to the overall antimicrobial effectiveness of the final drug product, then the data generated with the (b) (4) product may not be applicable to the 0.1 mg/mL product. Either provide data that demonstrates no antimicrobial effects are contributed by the dexmedetomidine hydrochloride or provide data that demonstrates that 0.1 mg/mL dexmedetomidine hydrochloride with the minimum preservative content, or below, meets the USP<51> requirements.

Please submit the information requested by email to me and Dr. Luz E. Rivera (Luz.E.Rivera@fda.hhs.gov) and officially submit to the application by **Friday, January 2, 2015**.

Please acknowledge and confirm receipt of this request.

Thank you,

Maya Johnson-Nimo
Lead Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
WO - BLDG 21, RM2672

Direct Phone: 301-796-5885

Blackberry: (b) (4)

E-mail: Maya.Johnson-Nimo@fda.hhs.gov

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, November 19, 2014 2:39 PM
To: 'Jeanne Squeglia'
Subject: RE: NDA 206628 dex micro IR

Considering our primary review timelines, we will need an earlier deadline for this request. This will need to be submitted before December holidays. I can extend the data by December 19th.

Allison

-----Original Message-----

From: Jeanne Squeglia [<mailto:jsqueglia@hqspecialtypharma.com>]
Sent: Wednesday, November 19, 2014 2:08 PM
To: Meyer, Allison
Subject: RE: NDA 206628 dex micro IR

Dear Allison

Thank you for your message below. We also received the same message from Luz E Rivera, Psy.D. (see below). Deadline stated was January 7, 2015. As November 25 is less than one week away, we will meet to original deadline provided.

Thank you,
Jeanne Squeglia

Sent: Monday, November 17, 2014 12:06 PM
To: Jeanne Squeglia
Attachments:

Good morning Mr. Pizza,

We are reviewing your New Drug Application 206628, dated May 12, 2014, and request additional information to continue our evaluation.

1. We refer to Module 3.2.P.2.2 Table 5. Antimicrobial effectiveness data should support the minimum preservative content in the specification. The product specification requires (b) (4) % of each preservative, which corresponds to a minimum of (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. The data provided in Table 5 do not support the proposed minimum specification for preservative content. Provide data that demonstrates that product with the minimum preservative content, or below, meets the USP<51> requirements.

2. We refer to the proposed package insert. Provide a maximum hold time for the diluted product prior to the start of the infusion. We recommend that this product be used immediately after dilution. Hold times in excess of 4 hours at room temperature or 24 hours under refrigeration should be supported with microbiological challenge data

Please officially submit to the application by January 7, 2015.

Please acknowledge the receipt of this request

Thank you,

Luz E Rivera, Psy.D.

LCDR, US Public Health Service

Sr. Regulatory Health Project Manager

FDA/CDER/OPS/ ONDQA

Division of New Drug Quality Assessment III

luz.e.rivera@fda.hhs.gov

301 796 4013

From: Meyer, Allison [Allison.Meyer@fda.hhs.gov]
Sent: Wednesday, November 19, 2014 11:19 AM
To: Jeanne Squeglia
Subject: NDA 206628 dex micro IR

Provide the following information or a reference to its location in the subject submission.

1. We refer to Module 3.2.P.2.2 Table 5. Antimicrobial effectiveness data should support the minimum preservative content in the specification. The product specification requires (b) (4) % of each preservative, which corresponds to a minimum of (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. The data provided in Table 5 do not support the proposed minimum specification for preservative content. Provide data that demonstrates that product with the minimum preservative content, or below, meets the USP<51> requirements.

2. We refer to the proposed package insert. Provide a maximum hold time for the diluted product prior to the start of the infusion. We recommend that this product be used immediately after dilution. Hold times in excess of 4 hours at room temperature or 24 hours under refrigeration should be supported with microbiological challenge data.

The above is due by November 25, 2014.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
12/03/2014

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Monday, November 17, 2014 12:06 PM
To: 'jsqueglia@hqspecialtypharma.com'
Subject: NDA 206628

Good morning Mr. Pizza,

We are reviewing your New Drug Application 206628, dated May 12, 2014, and request additional information to continue our evaluation.

1. We refer to Module 3.2.P.2.2 Table 5. Antimicrobial effectiveness data should support the minimum preservative content in the specification. The product specification requires (b) (4)% of each preservative, which corresponds to a minimum of (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. The data provided in Table 5 do not support the proposed minimum specification for preservative content. Provide data that demonstrates that product with the minimum preservative content, or below, meets the USP<51> requirements.
2. We refer to the proposed package insert. Provide a maximum hold time for the diluted product prior to the start of the infusion. We recommend that this product be used immediately after dilution. Hold times in excess of 4 hours at room temperature or 24 hours under refrigeration should be supported with microbiological challenge data

Please officially submit to the application by **January 7, 2015**.

Please acknowledge the receipt of this request

Thank you,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Sr. Regulatory Health Project Manager
FDA/CDER/OPS/ ONDQA
Division of New Drug Quality Assessment III
luz.e.rivera@fda.hhs.gov
301 796 4013

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, September 09, 2014 2:50 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628 micro requests

Provide the following information or a reference to its location in the subject submission:

1. We refer to the microbial ingress test conducted on the proposed container closure system. Provide the following information:
 - a. A description of the positive control vials
 - b. The incubation conditions (time and temperature) for the growth promotion units
2. We note that the manufacturing process does not include evaluation of the bioburden in the bulk solution (b) (4) (b) (4) Justify the lack of (b) (4) bioburden sample.
3. Provide the maximum hold time(s) for the bulk solution prior to (b) (4) process.
4. Provide a description of the environmental monitoring program. Include the media and incubation conditions as well as the proposed levels for viable and non-viable monitoring.
5. Provide the method verification studies for the sterility and endotoxin release tests.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
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/s/

ALLISON MEYER
09/09/2014

Meyer, Allison

From: Meyer, Allison
Sent: Friday, August 01, 2014 11:15 AM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: financial disclosure

Jeanne,
Provide a statement of financial disclosure to NDA 206628 by August 10, 2014.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Monday, July 07, 2014 4:17 PM
To: 'Jeanne Squeglia'
Cc: Stephanie Boffa
Subject: Patent certification issues

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 021038 for Precedex, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely. Specifically, your application does not contain a patent certification or statement with respect to patents that are listed in the Orange Book. Please submit an appropriate patent certification or statement with respect to these patents.

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021038&TABLE1=OB_Rx

Please note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to these patents, the certification is to be accompanied by a statement that you will comply with the requirements under 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 314.52(c) with respect to the content of the notice.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, June 24, 2014 3:55 PM
To: Jeanne Squeglia (jsqueglia@hqspecialtypharma.com)
Subject: NDA 206628

Below is the guidance we referred to during today's teleconference:

Guidance for Industry: *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>

Attendees:

Dr. Rigo Roca; Deputy Director
Dr. Chris Breder: Clinical Team Leader
Dr. Amelia Lockett: Clinical Reviewer
Dr. Adam Wasserman: Nonclinical Supervisor
Dr. Yun Xu: Clinical Pharmacology Team Leader
Dr. Julia Pinto: Pharmaceutical Assessment Lead
Dr. Xiaoben Shen: CMC Reviewer

And myself

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
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/s/

ALLISON MEYER
08/06/2014



NDA 206628

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

HQ Specialty Pharma Corporation
120 Route 17 North
Paramus, NJ 07652

Attention: Joseph Pizza
President

Dear Mr. Pizza:

Please refer to your New Drug Application (NDA) dated May 12, 2014, received May 12, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Dexmedetomidine Hydrochloride Injection, 400 mcg/4mL and 1000 mcg/10 mL.

We also refer to your amendments dated June 12 and July 1, 2014.

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 March 12, 2015.

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 February 13, 2015.

During our filing review of your application, we identified the following potential review issues:

1. In your proposed summary of the worldwide literature regarding Precedex in humans from 2008 to present, you placed 73 literature articles into categories. On initial review, these categories appear acceptable. However, you did not provide adequate detail to assess your comment that "review of these data did not identify any new risks" and that

labeling changes are not needed. You should report which adverse events noted in the literature already exist in the dexmedetomidine package insert and which do not so that we may evaluate the rationale for your recommendation.

Additionally, send us all literature articles used for your assessment.

2. You sent us a pediatric plan consisting of a waiver request for the procedural sedation indication. However, you have not provided sufficient evidence that “the product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.” Therefore, we disagree with your request for a waiver for neonates to pediatric patients less than 18 years of age.
3. Microbial testing should be included during stability at the 6-month and 12-month timepoints and yearly thereafter.

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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling 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:

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

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. The full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
07/24/2014

From: Jeanne Squeglia [mailto:jsqueglia@hqspecialtypharma.com]
Sent: Thursday, June 12, 2014 2:55 PM
To: Skarupa, Lisa
Cc: Meyer, Allison; Stephanie Boffa
Subject: Re: NDA 206628 request for proprietary name review

Dear Lisa,

We do not plan on using a proprietary name for this product. Please advise if you have any additional questions.

Best regards,

Jeanne Squeglia

From: Skarupa, Lisa
Sent: Thursday, June 12, 2014 2:34 PM
To: 'jsqueglia@hqspecialtypharma.com'
Cc: Meyer, Allison
Subject: NDA 206628 request for proprietary name review

Dear Jean Squeglia (HQ Specialty Pharma),

505b2 NDA#: 206628
Drug: dexmedetomidine hydrochloride injection
Subject: Proprietary Name Review

Your submission, dated May 12, 2014, provided no information regarding your plans to submit a request for a proprietary name review.
Please acknowledge this request for a clarification and a timeline for your response.

Sincerely,
Lisa

Lisa Skarupa, Senior Regulatory Project Manager | Office of Surveillance and Epidemiology
CDER | FDA | 10903 New Hampshire Avenue | Bldg 22, Room 4481 | Silver Spring, MD 20993
301.796.2219 (phone) | lisa.skarupa@fda.hhs.gov (email)

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/s/

LISA M SKARUPA
06/12/2014



NDA 206628

NDA ACKNOWLEDGMENT

HQ Specialty Pharma Corporation
120 Route 17 North
Paramus, NJ 07652

Attention: Joseph Pizza
President

Dear Mr. Pizza:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Dexmedetomidine Hydrochloride Injection, 400 mcg/ 4 ml and
1000 mcg / 10 ml

Date of Application: May 12, 2014

Date of Receipt: May 12, 2014

Our Reference Number: NDA 206628

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 July 11, 2014, 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 Anesthesia, Analgesia and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ALLISON MEYER
05/20/2014



PIND 119008

MEETING PRELIMINARY COMMENTS

HQ Specialty Pharma
120 Route 17 North, Suite 130
Paramus, NJ 07652

Attention: Joseph Pizza
President

Dear Mr. Pizza:

Please refer to your Pre-Investigational New Drug Application (PIND) file for dexmedetomidine hydrochloride injection.

We also refer to your June 27, 2013, correspondence, received June 28, 2013, requesting a meeting to discuss the proposed 505(b)(2) submission for dexmedetomidine hydrochloride injection.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



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

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: PIND
Meeting Date and Time: September 24, 2013 at 12:00 PM
Call in number: TBD
Application Number: PIND 118538
Product Name: dexmedetomidine hydrochloride injection
Indication: [REDACTED] sedation of non-intubated patients prior to and/or during surgical and other procedures
Sponsor Name: HQ Specialty Pharma

FDA Attendees	Title
Bob A. Rappaport, M.D.	Director
Rigoberto Roca, M.D.	Deputy Division Director
Christopher Breder, M.D., Ph.D.	Clinical Team Leader
Leah Crisafi, M.D.	Clinical Reviewer
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, DCP II
Olen Stephens, Ph.D.	Chemistry and Manufacturing Controls Lead, ONDQA
Adam Wasserman, Ph.D.	Supervisor, Pharmacology/Toxicology
Newton Woo, Ph.D.	Pharmacology/Toxicology Reviewer
Janice Derr, Ph.D.	Statistics Team Leader
Allison Meyer	Sr. Regulatory Health Project Manager

Sponsor Attendees	Title
[REDACTED]	Consultant, Pharmaceutical Development
Michele Scrofani	VP, Business Development
Jeanne Squeglia	VP, Technical
Stephanie Boffa	VP, Regulatory

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference

scheduled for September 24, 2013, at 12:00 pm between HQ Specialty Pharma and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

HQ Specialty Pharma is proposing to submit a marketing application through the 505(b)(2) regulatory pathway for dexmedetomidine hydrochloride injection with Precedex as the reference drug. The proposed indication will be for (b) (4)

sedation of non-intubated patients prior to and/or during surgical and other procedures. The Sponsor's formulation differs from the approved formulation in that it contains a preservative and one of the proposed presentations is diluted in a dextrose solution.

2. DISCUSSION

Regulatory/Medical

1. *Does the FDA concur with the overall content of the HQ Dexmedetomidine Hydrochloride Injection NDA based on Section 505(b)(2) of the FD&C Act?*

FDA Response: Yes, based on the content of your meeting package, we agree that the 505(b)(2) pathway is the appropriate pathway for your application.

2. *Does the FDA agree that the addition of parabens will not require additional clinical studies to support the approval of HQ dexmedetomidine HCl injection NDA based on Section 505(b)(2) of the FD&C act? Does the FDA agree that the submission [REDACTED] (b)(4) will not require additional clinical studies to support the approval of HQ Dexmedetomidine HCl injection NDA based on Section 505(b)(2) of the FD&C act?*

FDA Response: The Agency agrees that the addition of parabens to your dexmedetomidine drug product will not necessitate additional clinical studies if you provide adequate support for the excipients' safety at the concentrations and combination you have proposed. In the absence of adequate support for the safety of the proposed dose and use of parabens, nonclinical studies and a safety database of clinical exposures may be necessary. Likewise, the Agency agrees [REDACTED] (b)(4) should not necessitate additional clinical studies; however, refer to the response below and additional comments regarding the issue of extractables and leachables.

3. *Does the FDA concur with the difference in packaging material, which has been previously approved for other products, will not require additional nonclinical studies to support the filing and review for approvability of HQ Dexmedetomidine HCl [REDACTED] (b)(4) Injection NDA?*

FDA Response: No, we cannot agree at this time that additional nonclinical studies for the [REDACTED] (b)(4) injection formulation will not be required, since safety information regarding the new container closure system was not provided in the meeting package. You will need to provide adequate support from the use of these container closure systems in approved aqueous drug products. Otherwise, submit information on potential leachables and extractables for your drug products as soon as it is available so that, if necessary, the Agency can provide additional guidance on what qualification studies may be required for the NDA submission.

4. *Is the proposed nonclinical approach based up the review of the data from published literature, reference to FDA's previous determination of nonclinical safety and efficacy by reference to the Precedex Injection NDA 021038, sufficient to support a 505(b)(2) NDA filing for HQ's proposed Dexmedetomidine Hydrochloride Injection, for the proposed indication?*

FDA Response: Yes, your nonclinical approach based upon published literature and reference to the Agency's previous determination of safety and efficacy of the referenced drug appears sufficient to support a 505(b)(2) NDA filing for your drug product. However, additional nonclinical data may be necessary to

support the safety of the drug product formulation. Your NDA must include adequate information to support the safety of the drug substance impurities, drug product degradants, and the safety of the container closure system via an appropriate extractables and leachables safety assessment (see additional comments below).

5. *Does the FDA agree that the proposed levels of [REDACTED] (b)(4) will not require additional nonclinical studies for approvability of HQ Dexmedetomidine HCl Pharmacy Bulk Solution NDA?*

FDA Response: We agree additional nonclinical qualification studies are not required provided the level of [REDACTED] (b)(4) does not exceed 1% in the drug product (see additional comment #2 below). However, any impurity or degradation product that exceeds ICH thresholds as per ICH Q3A(R2), ICH Q3B(R2) must be adequately qualified for safety or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway.

Guidance for Industry: *Q3A Impurities in New Drug Substances*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

Guidance for Industry: *Q3B (R2) Impurities in New Drug Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

6. *Is the proposed clinical approach based upon the review of the data from published literature, reference to FDA's previous determination of clinical safety and efficacy by reference to the Precedex Injection NDA 021038, sufficient to support a 505(b)(2) NDA filing for HQ's proposed Dexmedetomidine Hydrochloride Injection for the proposed indications?*

FDA Response: Yes, your proposed approach is acceptable, [REDACTED] (b)(4) and you provide an adequate scientific "bridge" for those differences between your drug product and the reference drug. The bridge must provide evidence that the efficacy and safety are not compromised (see our answer to Question 7 for a discussion of this bridging evidence).

We have noted that in Section 2.1 of your proposed labeling (Appendix C), you have deviated from the Precedex labeling and extended the maximum infusion duration to [REDACTED] (b)(4) hours. However, the [REDACTED] (b)(4) hour duration in Section 2.1 is inconsistent with Section 1.1 of your proposed labeling and the content of the meeting package. It appears that your intent is to have identical labeling as Precedex and label for a maximum of 24 hours, in which case, you may rely, in conjunction with bridging evidence as described in the previous paragraph, on

the Agency's previous finding of safety of effectiveness for Precedex. If, however, you wish to increase in the maximum infusion duration, you will be required to provide substantial evidence of the safety and effectiveness of your drug administered at the proposed doses and new maximum duration.

7. *Does the Agency agree with the waiver of bioavailability or bioequivalence?*

FDA Response:

Your proposal for a biowaiver request for your proposed product is reasonable. However, the final determination of the acceptability of the waiver request for the CFR requirement to provide in vivo bioequivalence data for your proposed product will be made during NDA review.

We recommend that, in your NDA submission, you provide adequate scientific information/data supporting the bridging of your proposed product to the reference product with a side-to-side summary table comparing your proposed product to the reference product (including description, formulation, pH, osmolality, drug concentration, indication, etc.). For any difference(s) between your proposed product and the reference product, justify why this difference(s) would not affect the safety and/or effectiveness of your proposed product.

8. *It is HQ's intention to submit three registration batches, finished product release testing and stability data for the NDA filing. Stability data reported at the time of filing will consist of six months room temperature data and six months accelerated (40°C) data. An additional six months of room temperature stability data will be provided during the NDA review. The proposed expiration dating at the time of filing will be (b)(4) months. Does the Agency concur that this approach is adequate for filing and review for approvability of the NDA for Dexmedetomidine HCl (b)(4) injections and pharmacy bulk solution?*

FDA Response: No, your application should be filed with a complete stability package that includes at least 12 months of long-term stability data and 6 months of accelerated stability data as per the recommendations in ICH Q1A. You may submit stability updates after the NDA is filed, which will be reviewed as resources allow. However, we do not commit to reviewing stability updates submitted after filing the NDA.

9. *During manufacture of Dexmedetomidine HCl (b)(4) injection, we observe a manufacturing loss of approximately (b)(4)% of content. This difference was observed between (b)(4) samples. We intend to adjust the content of the active by approximately (b)(4)% to make up for the manufacturing (b)(4) (b)(4). Does the Agency agree with this approach?*

FDA Response: A targeted overfill may be appropriate for your manufacturing process if it is justified by data. Evaluation of your justification for the overfill will occur at the time of NDA review. Furthermore, you will need to clarify

whether the

(b) (4)

3.0 Additional Comments

1. For your NDA submission:

- a. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective and include:
 - i. *a genetic toxicology assessment*
 - ii. *a repeat-dose toxicology study of appropriate duration to support the proposed indication*

NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds.

- b. Provide extractables and leachables evaluations for all container closure components that contact the drug product solution. These evaluations should include specific assessments for residual monomers, solvents, polymerizers etc. Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system drug product formulation, dosage form, route of administration, and dose regimen. As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

For reference in how to design an extractables and leachables study, we refer you to the following PQRI publication:
http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

2. Note that there is only one set of regulatory specifications in an NDA submission. Your drug product must meet this set of specifications throughout the claimed product shelf life. However, it is permissible that you maintain an internal set of release specifications. In your application, this internal set of release specifications can be discussed as part of your overall control strategy.
3. We acknowledge the Preservative Effectiveness (PE) testing for the Pharmacy Bulk Vial submitted in the meeting package and have a comment for the development of the product. To document that the preservatives in the product are effective throughout the product shelf life; it is recommended that PE testing be performed on several concentrations of the preservatives. A bracketing approach can be used using concentrations at or below the lowest acceptable preservative concentrations for the product over the proposed shelf life of the product.
4. The meeting package states that the concentrated formulation is a pharmacy bulk pack. Pharmacy bulk packs do not have to be preserved and are to be used only by a pharmacist in a suitable work area such as a (b) (4). Since it is mentioned that a clinician may use the product, this would be a multi-use product rather than a pharmacy bulk pack. This will affect how the product will be labeled in the NDA.

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended*

Pediatric Study Plans at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

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

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

505(b)(2) REGULATORY PATHWAY

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

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

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies

described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

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

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

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

In addition to identifying 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)

<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

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 ANDA that cites the duplicate product as the reference listed drug.

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

/s/

ALLISON MEYER
09/23/2013