

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022432Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER  
008-372  
NAME OF APPLICANT / NDA HOLDER  
Questcor Pharmaceuticals, Inc.  
3260 Whipple Rd.  
Union City, CA 94587

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
H.P. Acthar® Gel

ACTIVE INGREDIENT(S) Corticotropin	STRENGTH(S) 80 Units per mL
---------------------------------------	--------------------------------

DOSAGE FORM  
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

*FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.*

*For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.*

**1. GENERAL**

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

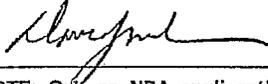
**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	June 16, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name David J Medeiros, VP Pharmaceutical Operations Questcor Pharmaceuticals, Inc.	
Address 3260 Whipple Rd	City/State Union City, CA
ZIP Code 94587	Telephone Number 510-400-0772
FAX Number (if available) 510-400-0799	E-Mail Address (if available) dmedeiros@questcor.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 022432

SUPPL # type 6 NDA

HFD # 120

Trade Name H.P.Acthar Gel

Generic Name recombinant corticotropin

Applicant Name Questcor Pharmaceuticals, Inc.

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

SE1

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

YES  NO

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

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

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?

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

H.P. Acthar Gel is a DESI upgrade product; however, the indication is not DESI.

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 #(s).

NDA# 008372

parent NDA for H.P. Acthar Gel

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 "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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>

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

pivotal efficacy study

Study CSR 222017-01 titled "High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study"

(Questcor obtained source efficacy data from this study and conducted their own analyses.)

supportive efficacy study

Study CSR 222017-04 titled, "High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms"

(Questcor obtained source efficacy data from this study and conducted their own analyses.)

supportive efficacy study

Study CSR 222017-05 titled, "Double-blind Study of ACTH versus Prednisone Therapy in Infantile Spasms"

(Questcor obtained source efficacy data from this study and conducted their own analyses.)

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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 <input type="checkbox"/>	! NO <input checked="" type="checkbox"/>
		! Explain:
		Studies not conducted under an IND.

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input checked="" type="checkbox"/>
		! Explain:
		Studies not conducted under an IND.

Investigation #3

IND #

YES

!  
!  
! NO   
! Explain:

Studies not conducted under an IND.

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

Investigation #1

YES

Explain:

!  
!  
! NO   
! Explain:

Studies from published literature.

Investigation #2

YES

Explain:

!  
!  
! NO   
! Explain:

Studies from published literature.

(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: Susan Daugherty

Title: Regulatory Project Manager  
Date: 10/5/10

Name of Office/Division Director signing form: Russell Katz, M.D.  
Title: Division Director

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

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

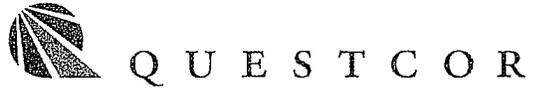
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/s/

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SUSAN B DAUGHERTY  
10/21/2010

RUSSELL G KATZ  
10/21/2010



### DEBARMENT CERTIFICATION

Questcor Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

In addition, to the best of Questcor Pharmaceuticals, Inc.'s knowledge, no person affiliated with Questcor Pharmaceuticals that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.

\_\_\_\_\_  
David J. Medeiros  
VP Pharmaceutical Operations  
Questcor Pharmaceuticals, Inc.

\_\_\_\_\_  
*June 16, 2006*  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022432 (type 6) BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: H.P.Acthar Gel Established/Proper Name: repository coticotropin Dosage Form: Gel for Injection		Applicant: Questcor Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Susan Daugherty		Division: Division of Neurology Products (DNP)
<p><b>NDA:</b>                      NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>October 30, 2010</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    NA May 6, 2007
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only):</p> <p><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 checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other talking points

<sup>2</sup> 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.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	included
--	----------

**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> )	Approval 10/15/10 Not Approvable Letter: 5/10/2007
---	---

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Agreed upon label 10/15/10
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	From resubmission: 12/10/09
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 6/18/10  
Reference ID: 2864298

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	See pg 5
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	See pg 5
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DRISK 9/24/10 <input checked="" type="checkbox"/> DDMAC 9/27/10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	5/17/07
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) 10/31/10
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes   X No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Indication</u></li> <li>• Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</li> </ul>	Pre IND advice: 3/27/2008 Correspondence: 4/21/2009 Correspondence: 6/1/2009 Inc. Resp. Ltr: 11/13/2009

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	Inc. Resp. Ltr: 12/10/2009 Inc. Resp. Ltr: 12/23/2009 Rev. Extension: 6/11/2010
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	End of Review conf: 11/9/2007
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	SPA response 3/27/08
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	May 6, 2010
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	Summary Minutes
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	X None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 05/10/07 and 10/15/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 05/10/07 and 9/27/10
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	05/10/07 and 9/27/10
• Clinical review(s) ( <i>indicate date for each review</i> )	04/24/07, 05/28/10, and 09/28/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	X 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> )	09/28/10 page 9 clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	DMEP PLR Review: 5/28/2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	9/29/10
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	7-21-2010 and 9-27-10
• 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 type="checkbox"/> None 9/24/10 and 9/27/10
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	X None requested

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 6/18/10  
Reference ID: 2864298

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	See Primary Review
Statistical Team Leader Review(s) (indicate date for each review)	See Primary Review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/5/2010
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	4/25/07, 11/19/07, 2/12/2009, and 10/01/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	X None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 03/08/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	none
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	6/1/2010
❖ Microbiology Reviews	X Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	X None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	10/31/06
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <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 checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> 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.



NDA 022432  
NDA 008372

**REMS NOTIFICATION**

Questcor Pharmaceuticals, Inc.  
Attention: Sian Bigora, Pharm.D.  
Vice President, Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for H.P. Acthar<sup>®</sup> Gel (repository corticotropin) injection.

In addition, we refer to our Risk Evaluation and Mitigation Strategy (REMS) notification dated July 21, 2010, and your proposed REMS submitted on August 12, 2010.

According to our REMS notification letter dated July 21, 2010 and in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P. Acthar Gel (repository corticotropin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation in pediatric patients being treated for infantile spasms.

Subsequent to our initial decision to require a REMS for H.P. Acthar<sup>®</sup> Gel (repository corticotropin), we have determined that the REMS for H.P. Acthar<sup>®</sup> Gel (repository corticotropin) should only apply to the infantile spasms indication for which you are seeking approval, and not to the multiple sclerosis indication or any of the existing approved indications. We have concluded that the patients who will be treated with H.P. Acthar<sup>®</sup> Gel (repository corticotropin) for infantile spasms are a uniquely vulnerable population, and that it is only for this indication that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. Our determination that this population is uniquely vulnerable is based upon both age and underlying disease suffered by patients with infantile spasms. These younger patients are more susceptible to infections and incapable of communicating symptoms associated with drug adverse reactions.

Therefore, amend your proposed REMS, including the Medication Guide, to address the infantile spasms population only.

Before we can continue our evaluation of this NDA, you will need to submit your amended proposed REMS.

Prominently identify your revised proposed REMS submission, with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022432 and NDA 008372**  
**PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send five copies of your REMS-related submissions.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Attachments: REMS and REMS supporting document templates

Appendix A: Medication Guide REMS Template

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide**

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

**B. Timetable for Submission of Assessments**

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, 18 months, three years and seven years from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B:

**REMS SUPPORTING DOCUMENT TEMPLATE  
MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
  - b. Describe in detail how you will comply with 21 CFR 208.24.
  - c. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

---

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

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/s/

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RUSSELL G KATZ  
09/27/2010

## REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:

**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)

REQUEST DATE

IND NO.

NDA/BLA NO.

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)

NAME OF FIRM:

PDUFA Date:

### TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**EDR link to submission:**

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

---

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

---

/s/

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SUSAN B DAUGHERTY  
09/16/2010

## REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:

**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)

REQUEST DATE

IND NO.

NDA/BLA NO.

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)

NAME OF FIRM:

PDUFA Date:

### TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**EDR link to submission:**

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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SUSAN B DAUGHERTY  
09/16/2010

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** August 31, 2010  
**TO:** NDA 22-432  
**FROM:** Colleen LoCicero, R.Ph.  
Associate Director for Regulatory Affairs  
Office of Drug Evaluation I  
**SUBJECT:** Change in regulatory classification of application from  
505(b)(2) to 505(b)(1)  
**APPLICATION/DRUG:** NDA 22-432 for H. P. Acthar Gel (repository corticotropin  
injection)

**Background:**

This application for use of H.P. Acthar Gel in the treatment of infantile spasms, received by FDA on June 23, 2006, was submitted as an efficacy supplement by Questcor Pharmaceuticals to NDA 8-372, reviewed in the Division of Metabolism and Endocrinology Products (DMEP).

On May 10, 2007, DMEP issued a Not Approvable letter for this supplemental application. The Not Approvable letter advised Questcor that, henceforth, the Division of Neurology Products (DNP) should have regulatory and scientific oversight of the application.

On November 9, 2007, Questcor met with DNP for an end-of-review conference to discuss next steps. On January 29, 2008, Questcor submitted a request for clinical Special Protocol Assessment (SPA) under pre-IND (b) (4). On March 27, 2008, DNP responded to the questions in the SPA submission and in an April 24, 2008, teleconference, Questcor and DNP came to agreement on the protocol in the SPA submission. Subsequently, Questcor submitted a revised protocol (on June 20, 2008).

Questcor submitted a response to the May 10, 2007, Not Approvable letter to DNP on November 26, 2008, but DNP determined that the submission did not constitute a Complete Response. Questcor submitted three more responses to the May 10, 2007 Not Approvable letter, dated March 13, October 15, and November 25, 2009, that DNP determined not to be Complete Responses as well. On December 10, 2009, Questcor submitted to DNP (received December 11, 2009) a response to the May 10, 2007 Not Approvable letter that DNP determined to be a Complete Response to the Not Approvable letter. With the receipt of this Complete Response, the application was redesignated a Type 6 NDA\* with a PDUFA goal date, for review of the Complete Response to the NDA, of June 11, 2010. This goal date was later extended to September 11, 2010 due to the receipt of a major amendment to the application.

**Regulatory Classification:**

Questcor designated the original efficacy supplement submitted to the Division of Metabolism and Endocrinology Products for this indication and the subsequent responses to the May 10, 2007, Not Approvable letter as submissions under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFD&C Act). The original efficacy supplement, which relied upon published literature to support approval of the application, was considered and reviewed as a 505(b)(2) supplement. It has been determined, however, by the 505(b)(2) review staff\*\* that, with the submission of the December 10, 2009 Complete Response, this application is a 505(b)(1) application, as the Complete Response contains source data from the investigator studies necessary to support approval of the application and does not rely on published literature.

As per Dr. Sheridan's review of this application, the clinical studies reviewed and relied upon by DNP to support the effectiveness of H.P. Acthar Gel in the treatment of infantile spasms are studies 222017-01, 222017-04 and 222017-05. All three studies were investigator-initiated studies. The data from these studies included in the Complete Response were obtained from the investigators' study records and from the charts of the patients included in the studies. The final study reports for these clinical studies that are included in the Complete Response were produced by Questcor, with the assistance of the study investigators.

The clinical studies reviewed and relied upon by DNP to support the safety of H.P. Acthar Gel in the treatment of infantile spasms are studies 222017-04, 222017-05, 222017-02, and QSC007-ACT-002. Studies 222017-02 and QSC007-ACT-002 provide new unpublished safety data obtained by Questcor from retrospective chart reviews.

In its review of this application, DNP relied upon the reports for these studies and their own analysis of the source data provided in the complete response. DNP did not rely on published literature or FDA's finding of safety and/or effectiveness of an approved application in reviewing the effectiveness and safety of H.P. Acthar Gel for the treatment of infantile spasms.

With respect to the nonclinical data that support this application, which is an efficacy supplement designated as a Type 6 NDA for administrative purposes, Questcor implicitly cross-references the nonclinical data in its previously approved 505(b)(1) application.

\*A Type 6 NDA is an efficacy supplement that is designated in CDER's database as a new NDA and assigned a new NDA number for administrative purposes (e.g., to facilitate the review of a supplement for an indication for which the scientific expertise lies in a division different from the parent division for the original application).

\*\*The 505(b)(2) review staff consists of representatives from CDER's Office of New Drugs (OND) Immediate Office, CDER's Office of Regulatory Policy, FDA's Office of Chief Counsel, and CDER's OND Associate Directors for Regulatory Affairs that meet on a regular basis to present and discuss pending 505(b)(2) applications and related issues.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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COLLEEN L LOCICERO  
08/31/2010



NDA 022432  
NDA 008372

**REMS NOTIFICATION**

Questcor Pharmaceuticals, Inc.  
Attention: Sian Bigora, Pharm.D.  
Vice President, Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for H.P. Acthar<sup>®</sup> Gel (repository corticotrophin) injection.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

H.P. Acthar Gel (repository corticotrophin) was approved on April 29, 1952, for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. We are now adding the indication of infantile spasms in pediatric patients. The known risks of infections and blood pressure elevation in MS patients have also been identified as risks in the pediatric population based on clinical trial data. Additionally, the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. The extension of the indication to pediatrics changes the risk benefit profile of H.P. Acthar Gel (repository corticotrophin) and is considered to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P. Acthar Gel (repository corticotrophin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that H.P. Acthar Gel (repository corticotrophin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The

Medication Guide is necessary for patients' safe and effective use of H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) is a product for which patient labeling could help prevent serious adverse effects, that H.P. Acthar Gel (repository corticotropin) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use H.P. Acthar Gel (repository corticotropin), and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed H.P. Acthar Gel (repository corticotropin).

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but is not limited to the following:

- a. An evaluation of patients' understanding of the serious risks of H.P. Acthar Gel (repository corticotropin)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication

Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022432 and NDA 008372  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022432 and NDA 008372  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Attachments

Appendix A: Medication Guide REMS Template

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name  
Address  
Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide**

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

**B. Timetable for Submission of Assessments**

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, 18 months, three years and seven years from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B:

**REMS SUPPORTING DOCUMENT TEMPLATE  
MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
    - b. Describe in detail how you will comply with 21 CFR 208.24.
    - c. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)
NDA-8372	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P. ACTHAR GEL

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/s/

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RUSSELL G KATZ  
07/21/2010



NDA 022432

**REVIEW EXTENSION –  
EFFICACY SUPPLEMENT**

Questcor Pharmaceuticals, Inc.  
Attention: Sian Bigora, Pharm.D.  
Vice President, Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your June 16, 2006 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We also refer to your December 10, 2009 submission containing a complete response to our May 10, 2007 action letter.

On June 9, 2010, we received your June 8, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 11, 2010.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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JACQUELINE H H WARE on behalf of RUSSELL G KATZ  
06/11/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): <b>Division of Metabolic and Endocrine Products</b> <b>Attn: Jena Weber, RPM</b>			FROM: <b>Division of Neurology Products</b> <b>Susan Daugherty, RPM</b>		
DATE 1-19-2010	IND NO.	NDA NO. 22-432	TYPE OF DOCUMENT PLR Converted labeling	DATE OF DOCUMENT 12-10-09	
NAME OF DRUG H.P. Acthar® Gel (repository corticotropin injection)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 5-7-2010	
NAME OF FIRM: Questcor Pharmaceuticals, Inc.					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): PLR conversion review					
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: NDA 22-432 provides for the use of Acthar Gel to treat infantile spasms. The sponsor has submitted a Complete Response that contains PLR converted labeling (current and proposed labeling are attached). We request that DMEP conduct the PLR content review. This application will go to AC 5-6-10 and the PDUFA goal date is June 11, 2010. The application is in the EDR and may be accessed at: <a href="#">\FDSWA150\NONECTD\N22432\N 000\2009-12-10</a>					
Thank you!					
SIGNATURE OF REQUESTER Susan Daugherty, RPM 6-0878			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

29 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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SUSAN B DAUGHERTY  
01/21/2010



NDA 22-432

**ACKNOWLEDGEMENT CLASS 2 RESPONSE**

Questcor Pharmaceuticals, Inc.  
Attention: David Young, Pharm.D., Ph.D.,  
Chief Scientific Officer  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Young:

We acknowledge receipt on December 11, 2009 of your December 10, 2009 resubmission to your supplemental new drug application for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We consider this a complete, class 2 response to our May 10, 2007 action letter. Therefore, the user fee goal date is June 11, 2010.

If you have any questions, call me at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

Susan Daugherty  
Senior Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

SUSAN B DAUGHERTY  
12/23/2009



NDA 22-432

**ACKNOWLEDGE INCOMPLETE RESPONSE**

Questcor Pharmaceuticals, Inc.  
Attention: Dave Medeiros  
Sr. Vice President, Pharmaceutical Operations  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Mr. Medeiros:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We acknowledge receipt on November 25, 2009 of your November 25, 2009 submission to your supplemental new drug application for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We do not consider this a complete response to our action letter because the definition file for the study 05 datasets is not entirely readable. Therefore, the review clock will not start until we receive a complete response.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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RUSSELL G KATZ  
12/10/2009



NDA 22-432

**ACKNOWLEDGE INCOMPLETE RESPONSE**

Questcor Pharmaceuticals, Inc.  
Attention: Dave Medeiros  
Sr. Vice President, Pharmaceutical Operations  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Mr. Medeiros:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We acknowledge receipt on October 15, 2009 of your October 15, 2009 submission to your supplemental new drug application for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

Please also refer to the teleconference between representatives of Questcor Pharmaceuticals and representatives from the Division of Neurology Products on November 4, 2009. During that teleconference we notified you that your submission was not a complete response to our action letter because the definition files do not provide enough detail for review and some of the links to case report forms (CRFs) are incorrect. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies need to be addressed:

- Include an explanation in the definition file when the variable name in two different datasets is the same but does not represent the same data.
- Clearly define the variables. If a variable is for testing purpose rather than analysis, please clearly state that. If a variable is a derived variable, we recommend that you include a brief algorithm in the definition file.
- Correct links to the Case Report Forms.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

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RUSSELL G KATZ  
11/13/2009



NDA 22-432

Questcor Pharmaceuticals, Inc.  
Attention: Steven Halladay, Ph.D.  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We also refer to the teleconference between representatives from Questcor Pharmaceuticals and the Division of Neurology Products on May 12, 2009, to discuss the resubmission of your NDA. We further refer to your electronic mail correspondences dated April 30, 2009 (containing an email from Dr. Hrachovy dated April 29, 2009), and May 7, 2009 (proposing a Statistical Report to supplement the 1994 Hrachovy study report) which are appended.

The following points were agreed upon during the May 12, 2009 teleconference:

- You will provide a new Statistical Report (serving as an addendum to the original Hrachovy [1994] study report). This will contain a new primary analysis of the primary endpoint that will examine the modified intent to treat (mITT) set, which will include all patients who received drug and have a recorded primary endpoint. Subset mITT analyses by gender, etc, must also be redone to include the previously missing patients. The Statistical Report will also repeat all the secondary endpoint analyses which had been previously done on the 50 patients now done on the revised mITT set.
- Newly recovered data must be incorporated into old datasets and must be presented as a single dataset.
- As a type of sensitivity analysis, an evaluation of the full ITT population of 59 patients must be performed. This analysis must include the mITT set and all remaining patients where there is no outcome data. A “worst case scenario” must be imputed for the patients where no outcome data exists such that the high-dose patients are considered to be nonresponders and the low-dose patients are to be considered responders.
- Patient narratives must be provided for patients #IX13, IX20, IX25, IX26 (including information about the infectious disease consultation report discussing the role of ACTH in the terminal illness), and IX 50.
- The original study report for the Hrachovy (1994) study, as previously submitted, does not have to be revised and will serve as a *per protocol* analysis of the 50 patients who completed the study.

- The new submission must have rewritten, comprehensive higher level summaries (ISE, ISS, and clinical summary) which should be revised so that the text and tables integrate the newly generated data on the missing patients with the efficacy and safety data previously submitted.
- The new submission must be submitted in the eNDA format as was done on March 13, 2009. There is no need to withdraw the March 13, 2009 submission.
- The new submission must be free-standing and comprehensive, incorporating all the previously submitted data and analyses (including those from the Baram and Hrachovy [1983] pivotal studies) as well as all the components detailed above.
- The Agency asks to be notified about one month prior to this resubmission

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

**Daugherty, Susan B (CSO)**

---

**From:** [REDACTED] (b) (4)  
**Sent:** Thursday, April 30, 2009 10:02 PM  
**To:** Daugherty, Susan B (CSO)  
**Cc:** DBailey@questcor.com; Medeiros, David; Dempsey, David; [REDACTED] (b) (4); Choi, Young; [REDACTED] (b) (4)  
**Subject:** NDA 22-432\_Study-05\_Analysis Ongoing and Letter from R Hrachovy  
**Attachments:** R Hrachovy Ltr to QSC\_4.29.09.pdf

Dear Susan,

In follow up to our recent emails and telephone discussions, we provide the attached letter from Dr. Richard Hrachovy from the Baylor University College of Medicine. This letter describes the diligence performed by him to locate the nine charts from patients who enrolled in the high dose-low dose Acthar study, but discontinued the study prior to study completion. Dr. Hrachovy was able to locate eight of the nine charts; further details are in his attached letter. As he indicated, Dr. Hrachovy is available to discuss these data with the Agency at your discretion.

Dr. Hrachovy did not recall until he reviewed these charts that one of these eight patients died after being enrolled into the study from complications thought unrelated to treatment with Acthar Gel. Questcor was informed of this finding on Tuesday, April 28, 2009, in a teleconference with Dr. Hrachovy. This was the first notification to Questcor of this event. Questcor is presently preparing the required expedited safety report (MedWATCH) and will submit this report as required.

Questcor is currently initiating a thorough review of these additional data. We will submit our plan to the Agency next week for updating the Complete Response; we would like to submit these to you via email. We would appreciate your feedback on our proposed plan by whichever mechanism is preferable to you (e.g., email, telephone discussion).

Please feel free to contact [REDACTED] (b) (4) for Questcor (at [REDACTED] (b) (4) mobile or via email at [REDACTED] (b) (4)), or me (at [REDACTED] (b) (4) mobile or reply to this email) if any additional information is needed.

Thank you,

[REDACTED] (b) (4)

(b) (4)





Baylor College of Medicine

**PETER KELLAWAY SECTION**

**OF NEUROPHYSIOLOGY**

Department of Neurology

ONE BAYLOR PLAZA, SUITE NB302

HOUSTON, TX 77030

713-798-0980 (Phone)

713-798-0984 (FAX)

April 29, 2009

Steven Halladay, Ph.D.

Senior Vice President, Clinical and Regulatory Affairs

Questcor Pharmaceuticals, Inc.

3260 Whipple Road

Union City, CA 94587

Dear Dr. Halladay:

I am writing this letter to Questcor following an inquiry by the U.S. Food and Drug Administration (FDA) regarding the availability of the charts for the 9 patients who withdrew from our study.<sup>1</sup> As was noted in our publication, these nine patients, four randomized to the high-dose group and five randomized to the low dose-group, "were excluded from final analysis because they did not complete the treatment protocol for various reasons, including compliance problems, moving from the area before the protocol was completed, or the development of medical problems unrelated to use of ACTH but, in, the opinion of the investigators, precluded the continued use of ACTH".<sup>1</sup> I also understand that FDA inquired as to whether we had performed any analyses that included more than the 50 patients in the publication, up to and including all 59 patients who enrolled into the trial or whether any other sources of study data (e.g., spreadsheets or other data sources) might still be available.

Regarding the availability of the patient charts, over the last week, I was able to secure several boxes; these boxes should have contained all of the study charts from Baylor

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<sup>1</sup> Hrachovy RA, Frost JD, Glaze DG. High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms. *J Pediatr* 1994;124:803-806.

College of Medicine's storage facility. To my knowledge, this is the only possible source of the charts for these patients. I was pleased to find the study charts for 8 of these 9 patients who did not complete the study. These data have been photocopied and were sent to you by overnight delivery on April 28, 2009.

The following table summarizes the pertinent information for these 8 patients.

Pt #	Randomization (Low: ACTH 20 U/day; High: ACTH 150U/m2/day)	Study Treatment Duration	Reason for Study Discontinuation
IX-13	High	2 weeks	Parents refused to continue protocol
IX-20	High	Up to 3 weeks (Estimated)	Patient moved from state
IX-25	Low	6 weeks	Parents refused final monitoring
IX-26	Low	See narrative below	See narrative below
IX-34	High	None	Parents refused to start study treatment after randomization
IX- 42	High	None	Study treatment delayed due to medical condition. Spasms stopped before treatment started-spontaneous remission
IX-49	Low	None (Estimated)	Parents refused study treatment after randomization
IX-50	Low	1 day (Estimated)	Study treatment stopped because of fever and irritability
IX-58	Low	Unknown	Unknown

Regarding Patient IX-26, this was a 3 month old male with severe developmental delay and a history of seizures since 3 days of age. The patient was seen by Dr. (b) (4), a co-investigator, at the (b) (4) the patient was enrolled into the study and was randomized to the low dose ACTH regimen. Thereafter, the patient was treated by his local physician in (b) (4). Following 2 weeks of ACTH treatment (at a dose of 20 units/day), the patient returned to (b) (4) for EEG monitoring; at that time he still had spasms. His dose of ACTH was increased to 30 units/day and he returned to (b) (4). Shortly thereafter, he developed respiratory problems which were treated by physicians in (b) (4). Unfortunately, he did not recover from his illness and died from respiratory failure. At the time, Dr. (b) (4) and the infectious disease consultants did not believe that ACTH contributed to

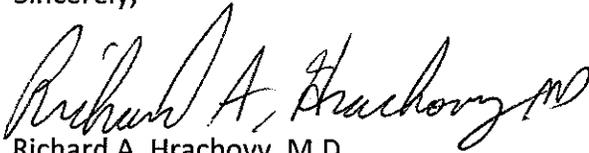
the patient's death because of the severity of the patient's underlying medical problems. The patient's death was reported to the IRB. Subsequently, the patient's chart was inadvertently filed away with the charts of other patients who did not complete the protocol (listed above). When the publication of this study was being prepared several years later, we apparently did not remember this patient and consequently did not mention him in the paper.

Regarding the chart for patient IX-58, unfortunately, it was not contained in the archived boxes. This final chart, is, therefore, not locatable; its absence from the archival record storage facility means that the chart is lost. In addition, I also want to clarify that all original EEG records for the 59 patients enrolled in this study were stored in the basement of [REDACTED] (b) (4) and were destroyed when the basement was flooded during Tropical Storm [REDACTED] (b) (4) in 2001.

I would also like to confirm that there are no other known sources of data for this study. I am aware of no data files containing data from all 59 patients. In addition, no analyses were ever conducted that included all 59 patients who enrolled in the study. We did not conduct a Modified-Intent-To-Treat analysis or any other analyses that included all 59 patients randomized into the study.

I understand the importance of FDA's request for the additional data and would like to offer my continued assistance to them. Please let the officials at FDA know that I would be happy to discuss the details of this study with them, its conduct and data collection, as well as the analysis of the data and our conclusions.

Sincerely,



Richard A. Hrachovy, M.D.  
Professor of Neurology  
Head, Peter Kellaway Section of Neurophysiology  
Baylor College of Medicine  
One Baylor Plaza  
Houston, Texas 77030  
Telephone: 713-798-0980  
Email-hrachovy@bcm.edu

**Daugherty, Susan B (CSO)**

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**From:** (b) (4)  
**Sent:** Thursday, May 07, 2009 8:13 PM  
**To:** Daugherty, Susan B (CSO)  
**Cc:** Bailey, Don; (b) (4); Medeiros, David; Dempsey, David; Choi, Young;  
**Subject:** NDA 22-432\_5.7.09\_Acthar Gel: Proposal for Statistical Report: Study 222017-05B

**Hi Susan,**  
**Please forward this message to Dr. Katz:**

Dear Dr. Katz:

Reference is made to our teleconference with your colleagues and you on 9 April 2009 and the subsequent efforts made by Dr. Hrachovy to locate the charts of the nine additional patients who enrolled into his study. (Hrachovy RA et al. High-dose, long duration versus low-dose, short duration corticotrophin therapy for infantile spasms. J Pediatr 1994;125:803-6.) Reference is also made to our submission of a letter from Dr. Hrachovy on 30 April 2009 where he describes his efforts to locate the nine charts from the patients, all of whom were reported to have discontinued the study prior to study completion. As he reported in his letter, eight of these nine charts were locatable.

Questcor has obtained redacted copies of the above-mentioned eight charts. The data are being processed in an identical fashion as the data from the first 50 patients from this study: the charts are undergoing transcription into Case Report Forms and the data will then be entered into the study database.

Questcor is, therefore, proposing the following:

- A Statistical Report (entitled, Questcor Statistical, #222017-05B) will be submitted to the Agency consisting of the following:
  - A Statistical Analysis Plan for a modified Intention to Treat (mITT) analysis of the entire patient dataset from the study
  - Tables and listings of the demographic, baseline and efficacy data for the mITT analysis
  - A listing of the adverse event data from the additional eight patients
  - SAS datasets of the mITT data (complete, baseline, efficacy and safety).
- A comprehensive safety update will be submitted to the sNDA to include the safety data from these additional patients as well as any additional safety data that Questcor may obtain through postmarketing surveillance or other means. Based on our earlier conversations with the Agency, this update will likely be submitted sooner than the traditional 120-day safety update. A discussion as to the date the Agency would like this update submitted would be appreciated.

Questcor believes that the submission of the Statistical Report will provide the full information on these additional patients, with data integration from the data from the other 50 study patients, via the mITT analyses. We believe this Report will enable the Agency to fully assess this study and, further, we believe this Statistical Report should allow the Agency to designate our sNDA submission to be a full Complete Response. This Statistical Report is scheduled to be available for transmission to the Agency on 22 May 2009 via email and/or electronic media. (b) (4) will communicate with Susan Daugherty on the particulars for the operational transmission of this submission.

Questcor is working to deliver this Statistical Report as described above concurrent with awaiting the Agency's concurrence with this plan. We respectfully request a brief telephone discussion with the Agency at your earliest convenience over the coming several business days, or, request a reply to this proposal in an expeditious manner. If you have any questions or need additional information, please contact either, (b) (4), at (b) (4) or (b) (4) to Questcor at (b) (4).

We appreciate your prompt attention.

Thank you.

(b) (4)

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/s/

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Eric Bastings  
6/3/2009 05:51:09 PM



NDA 22-432

Questcor Pharmaceuticals, Inc.  
Attention: Steven Halladay, Ph.D.  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

Please also refer to the teleconference between representatives of Questcor Pharmaceuticals and representatives from the Division of Neurology Products on April 9, 2009. During the April 9<sup>th</sup> teleconference we notified you that your submission was not a complete response to our action letter because data was missing for 9 patients in one of the pivotal studies. In order to correct this we ask you perform a thorough search for the missing data. If such data remains missing you must describe what efforts were made to search for the missing data and include a complete, and well documented, explanation of the reason the data is missing. This should include a formal detailed statement from the individual investigator.

Therefore, the review clock will not start until we receive a complete response.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Russell Katz

4/21/2009 05:08:03 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-432

Questcor Pharmaceuticals, Inc.  
Attention: Steven Halladay, Ph.D.  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar<sup>®</sup> Gel (repository corticotropin injection).

We do not consider this a complete response to our action letter, because we are not able to perform a review of your application in its present electronic format, and your application contains files that are not in conformance with FDA's specifications (e.g. .xls files or Zip files). Therefore, the review clock will not start until we receive a complete response.

Please re-submit your response in a format that is in conformance with FDA specifications. You may contact [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) if you require assistance with the appropriate electronic formatting.

If you have any question, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Russell Katz  
12/23/2008 08:12:53 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR CONSULTATION

TO (Division/Office): Biometrics HFD-710

FROM: Division of Neurology Products,  
Susan Daugherty, (301 796-0878)

DATE December 3, 2008

IND. NO.  
(b) (4)

NDA NO.  
**22-432**  
**(08-372/S-039)**

TYPE OF DOCUMENT  
Complete Response to NA

DATE OF DOCUMENT  
November 26, 2008

NAME OF DRUG  
Acthar Gel

PRIORITY CONSIDERATION  
High

CLASSIFICATION OF DRUG  
AED – Infantile Spasms

DESIRED COMPLETION DATE  
May 28, 2008

NAME OF FIRM: Questcor

### REASON FOR REQUEST

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
PROTOCOL REVIEW  
OTHER (SPECIFY BELOW):

CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

COMMENTS/SPECIAL INSTRUCTIONS: **Please review and this Complete Response to NA**

SIGNATURE OF REQUESTER  
Susan Daugherty, Regulatory Project Manager

METHOD OF DELIVERY (Check one)  
 MAIL  HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Susan B. Daugherty  
12/3/2008 05:08:43 PM

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** August 8, 2008

**SUBJECT:** Creating Type 6 NDA

NDA 08-372/S-039 was submitted to and reviewed by the Division of Metabolic and Endocrine Products. However, it should have been reviewed by the Division of Neurology Products as a type 6 NDA because the indication is for infantile spasms.

Therefore, sNDA 08-372/S-039 has been converted to the new NDA 22-432 for the 2nd cycle.

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/s/

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Susan B. Daugherty  
8/8/2008 02:45:50 PM  
CSO



PIND (b) (4)

Questcor Pharmaceuticals, Inc.  
Attention: Steven Halladay, Ph.D.  
Senior Vice President, Clinical and Regulatory Affairs  
3260 Whipple Road  
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your pre-Investigational New Drug Application (PIND) received on January 29, 2008, for Acthar<sup>®</sup> Gel. This submission contains a clinical Special Protocol Assessment request. The protocol is titled "Determination of the Adverse Effect profile for Patients with Infantile Spasms Treated with HP Acthar Gel (ACTH); A Retrospective Review."

We have completed our review and, based on the information submitted, have the following responses to your questions. Our responses are bolded and follow each question.

1. Disease: The protocol proposes to access the charts of patients diagnosed with infantile spasm (IS). Other diagnosed epileptic encephalopathies are not part of the intended population, or the Acthar Gel package insert. Does the Agency agree with this proposal to limit the charts to patients with IS?

**Yes, because infantile spasm is the indication under consideration in supplemental new drug application NDA 08-372/S-039.**

2. Patient Age: The protocol proposes to assess charts of patients in the age range of 3 months to 2 years old. The basis is that for patients aged below 3 months, there is often a different neurological syndrome involved and that may result in clinical outcomes and toxicities that are not representative of this condition. Acthar Gel is not intended for use in patients over 2 years old. Does the Agency agree with this proposal for the age range of minimum 3 months and maximum 2 years?

**Yes, this age range would include the vast majority of infants presenting with infantile spasms. The protocol text needs to make explicit the minimum age of 3 months.**

3. First Use of Acthar Gel: The protocol proposes to assess charts of patients who were naïve to treatment with Acthar Gel. This first use of Acthar Gel will provide information relevant to the proposed package insert. Experience other than first use will be included in discussion in the ISS in the Complete Response as available from literature and other sources. Does the Agency agree?

**No, the Agency requests that the charts of patients who receive Acthar Gel other than first use (e.g. second course of therapy for partial responder to the first course) also be assessed as part of the retrospective study if their treatments occurred in the proposed 2002-2007 time period at the participating centers. The literature and other sources cannot be relied on for complete safety data in the “other than first use” patients just as they cannot be relied on for the first-use patients. This information will still be of interest even if you intend to label for a single course of treatment.**

4. Dose of Acthar Gel: The prospective protocol plan will assess patients having the dosing schedule of approximately 150 IU/sq.m./day in equally-divided BID doses of 75 IU/sq m. This usage will most closely reflect the proposed package insert for Acthar Gel. A separate literature review of experience with Acthar Gel at other doses, including discussions on the overall efficacy and safety of Acthar Gel at various doses, will be included in the Complete Response. Does the Agency agree with this proposal for the dose of the retrospective safety study?

**No, the Agency requests that the charts of patients who receive Acthar Gel by other dosing schedules (e.g. lower dose, higher dose, QD, etc.) also be assessed as part of the retrospective cohort study if their treatments occurred in the proposed 2000-2007 time period at the participating centers. The literature and other sources cannot be relied on for complete safety data in the “other dosing schedule” patients just as they cannot be relied on for the patients dosed at 150 IU/sq.m./day in equally-divided BID doses. The vast majority of patients however should be exposed to doses at or higher than the intended labeled daily dose. A separate analysis should be performed for patients that are exposed to the anticipated labeled dosage.**

5. Denominator and Date Range for Charts: For the prospective safety analysis of this protocol, we propose to access charts in reverse chronological order beginning with 2007 and going back to 2002 with the objective to identify approximately 100 applicable charts from patients fitting the inclusion criteria (approximately 150 IU/sq .m/day in equally divided BID doses of 75 IU/day) identified above. All applicable charts beyond the initial 100 will also be accessed and analyzed for inclusion with the applicable safety updates to the NDA. Does the Agency agree with these proposals for the denominator of N= 100 for the analysis, and the overall chart review plan?

**The Agency requests that all charts fitting the inclusion criteria be accessed rather than stopping after the first 100 charts, as noted in the question. Then, continue on until 200 charts are accrued which meet the criteria and are considered evaluable. Please note there is an inconsistency in your present proposal: i.e. the protocol on page 6 [15] indicates a planned sample size of 150.**

In addition, we have the following comments.

1. Please indicate whether both American and foreign centers will participate.
2. Please clarify in the exclusion criteria #2 (page 6 [15]) whether infants who previously received short-term steroids for asthma, bronchiolitis, etc. will be included. It would seem appropriate that they would be included.

3. The “final visit” for each patient is defined as the first visit after the last dose administered. The final visit should be at least 2 weeks after the last dose administered to allow assessment of late developing adverse effects.
4. The definition of serous adverse effect (page 9 [18]) should also include life-threatening AE, AE resulting in permanent disability, and AE requiring extension of hospitalization.
5. Complete patient narratives should be provided for patients with serious adverse effects or who discontinued the Acthar gel due to adverse events.
6. Analysis of all laboratory data (including EKGs when available) and vital signs should include shift tables (e.g. normal to abnormal shifts), central tendency analysis (e.g. mean and median) and analysis of marked outliers.
7. We note that you are evaluating adverse events through inferential statistics. This is acceptable, however, as this study is not powered for such an analysis and there are no corrections for multiple comparisons, we consider such an analysis as exploratory. We will largely rely on the descriptive statistical analysis.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the “*Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products*”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

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

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

QUESTCOR  
PHARMACEUTICALS  
INC

H.P. ACTHAR GEL

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/s/

RUSSELL G KATZ  
03/27/2008

## Weber, Jena M

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**From:** Joffe, Hylton  
**nt:** Tuesday, August 08, 2006 2:23 PM  
**To:** Weber, Jena M  
**Subject:** Acthar gel - comments for 45d filing letter

Hi Jena,

Here are my comments to Questcor:

1. We have been unable to locate the "define" file for the variables used in the dataset. Please send this document or let us know where we can find the information in the original submission.
2. Please provide a Microsoft Word version of the proposed labeling text as well as a Word version with tracked changes.

Thanks,

Hylton