

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-212

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-212

SUPPL #

HFD # 520

Trade Name Durezol

Generic Name difluprednate ophthalmic emulsion, 0.05%

Applicant Name Sirion Therapeutics, Inc.

Approval Date, If Known June 23, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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?

5 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

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#

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 NO

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

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

Investigation #1 YES NO

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

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

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

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

Investigation #1 !
IND # YES ! NO

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

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

(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: Jane A. Dean, RN, MSN
Title: Regulatory Health Project Manager
Date: 6/24/08

Name of Office/Division Director signing form: Wiley A. Chambers, MD
Division of Anti-Infective and Ophthalmology Products
Title: Acting Director

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

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-212 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A
Division Name: DAIOP PDUFA Goal Date: 6/26/08 Stamp Date: 12/26/2007

Proprietary Name: Durezol

Established/Generic Name: difluprednate ophthalmic emulsion 0.05%

Dosage Form: topical ophthalmic emulsion

Applicant/Sponsor: Sirion Therapeutics

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) N/A
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMC #: _____

Does the division agree that this is a complete response to the PMC?

- Yes. **Skip to signature block.**
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): _____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of inflammation and pain associated with ocular surgery.

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for the remaining pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
Population	minimum	maximum						
<input type="checkbox"/> Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	__ yr. <u>0</u> mo.	<u>3</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): <u>6/26/2011</u>								

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	__ yr. __ mo.	__ yr. __ mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	3 yr. 11 mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jane A. Dean, RN, MSN
Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

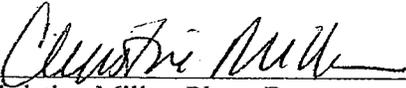
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jane Dean
6/24/2008 11:00:58 AM

1.3.3 Debarment Certification

Sirion Therapeutics, 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.



Christine Miller, PharmD
Senior VP of Drug Development

14 November 2007
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-212 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Durezol Established Name: difluprednate ophthalmic emulsion, 0.05% Dosage Form: ophthalmic emulsion		Applicant: Sirion Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Jane A. Dean, RN, MSN		Division: 520
<p>NDAs: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(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 here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		June 26, 2008
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR <input type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

¹ 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 ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input type="checkbox"/>	5/28/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ 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	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? 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. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (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.) 	<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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<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>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	X
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/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 6/23/08
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	n/a
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	5/15/08
❖ Original applicant-proposed labeling	12/21/07
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	n/a

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/19/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	6/23/08
❖ Original applicant-proposed labeling	12/21/07
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	n/a
❖ Most recent applicant-proposed labeling	5/19/08
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 6/3/08; 6/23/08 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 5/6/08 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (<i>indicate date of each review</i>)	4/25/08
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ 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>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input type="checkbox"/> None 5/1/08 5/8/08; 6/5/08
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Regulatory Briefing (<i>indicate date</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> Not applicable 5/27/08 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 9/24/07 <input type="checkbox"/> No mtg 10/6/08

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 5/19/08

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	5/29/08
• 48-hour alert or minutes, if available	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/23/08
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/23/08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/23/08
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	see CDTL Review
• Clinical review(s) (<i>indicate date for each review</i>)	6/4/08
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Clinical Review 6/4/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Clinical Review 6/4/08
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	6/4/08; 6/23/08
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/10/08
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/10/08
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/23/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/19/08

Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/9/08
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 5/12/08
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/6/08; 6/9/08
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/4/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 5/7/08
❖ 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	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/4/08
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 5/28/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	5/12/08; 6/9/08, 6/23/08 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	5/28/08
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: 1/31/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs:	
> TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
> Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (date completed must be within 60 days prior to AP)	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
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Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Jane Dean

6/24/2008 10:56:24 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 23, 2008

TO: Jane Dean, Regulatory Project Manager
Sonal Wadhwa, Medical Officer

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-212

APPLICANT: Sirion Therapeutics, Inc.

DRUG: Difluprednate ophthalmic emulsion, 0.05% (Durezol)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review

INDICATIONS: Treatment of pain and inflammation following ocular surgery

CONSULTATION REQUEST DATE: January 30, 2008

DIVISION ACTION GOAL DATE: May 26, 2008

PDUFA DATE: June 26, 2008

I. BACKGROUND

This brief note updates the previous clinical inspection summary (DFS date 6-5-2008) to include the preliminary results of the sponsor inspection. The updated sponsor inspection result is shown in the table below (item 3, Sirion Therapeutics, Inc., Tampa, Florida), and the inspectional findings are summarized under "Addendum."

II. INSPECTION RESULTS

	Name of CI or Sponsor City and State/Country	Protocol Site Number Subjects	Inspection Dates	Classification	
				Interim	Final
1	Steven M. Silverstein, MD Silverstein Eye Centers Kansas City, Missouri	ST - 601A - 002b site 0030 38 subjects	5/5/08 - 5/9/08	NAI	pending
2	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. Washington, Missouri	ST - 601A - 002b site 0034 58 subjects	5/12/08 - 5/16/08	NAI	pending
3	Sirion Therapeutics, Inc. Tampa, Florida	ST - 601A - 002a ST - 601A - 002b	6/9/08 - 6/12/08	NAI	pending

NAI = no action indicated / no deviations from regulations; VAI = voluntary action indicated / no significant deviations from regulations; OAI = official action indicated / significant deviations from regulations; NA = not applicable

Addendum

3. Sirion Therapeutics, Inc., Tampa, Florida:

The regulatory files for all clinical sites were examined. The regulatory files for the two previously inspected clinical sites (sites 0030 and 0034, items 1 and 2 in the table above) were consistent with the inspectional findings at those sites. No significant deficiencies were observed at the sponsor inspection, and the inspection did not reveal any findings that suggested compromised data integrity.

Observations noted above are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of two US clinical sites in addition to the sponsor inspection. The deficiencies noted at the two clinical sites were minor in nature and appeared to be isolated occurrences. The overall inspection results support the validity of the data submitted by the sponsor under this NDA.

The formal EIRs from the three inspections remain pending as of the date of this addendum. Further addendum will be issued if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

/s/

John Lee
6/23/2008 01:11:18 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
6/23/2008 01:16:13 PM
MEDICAL OFFICER

SIRiON

Therapeutics

June 10, 2008

Wiley Chambers, MD
Acting Director
US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-212 (0011)
Difluprednate Ophthalmic Emulsion, 0.05% (ST-601)
Efficacy Information Amendment

Dear Dr. Chambers:

Reference is made to Sirion Therapeutics, Inc. New Drug Application 22-212, submitted on December 21, 2007. By way of this amendment Sirion commits to conduct a post-marketing study of difluprednate in pediatric patients as described herein.

This amendment is approximately 189 KB in size and the corresponding updated application sections are on a CD.¹ The enclosed information has been formatted to eCTD specifications.

If you have any questions regarding this submission or require any additional information, please contact me directly by telephone at (813) 496-7325, extension 236, by e-mail at cmiller@siriontherapeutics.com, or by fax at (813) 496-7328.

Sincerely,



Christine Miller, PharmD
Sr VP, Drug Development
Sirion Therapeutics, Inc.

¹ Sirion certifies that the files on the CD are virus free and have been scanned with TREND MICRO™ Client/Server Security Agent Version 7.6.1161.

1 Page(s) Withheld

 X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1

Dean, Jane

From: Christine Miller [cmiller@siriontherapeutics.com]
Sent: Thursday, June 05, 2008 11:01 AM
To: Dean, Jane; Chambers, Wiley A
Cc: Barry Butler; Kim McLeod; Roger Vogel (aol)
Subject: NDA 22-212 Difluprednate Ophthalmic Emulsion, 0.05% Post-marketing commitment re Pediatric Study - Revised June 5, 2008

Dear Dr. Chambers,

Sirion commits to conducting a post-marketing study of difluprednate in pediatric subjects as described below. A formal electronic NDA amendment will be submitted within the next few business days.

o *Type of study:*

o *Indication(s) to be studied:* Treatment of post-operative inflammation following cataract surgery.

o *Age group in which study will be performed:* Pediatric patients aged 0 to 3 years of age undergoing cataract surgery.

o *Number of patients to be studied:*

o *Study endpoints:*

o *Drug information:*

o *Drug specific safety concerns:*

6/5/2008

- o *Statistical information, including power of study and statistical assessments:*

5

Protocol Submission Date: 10/26/2008
Study Start Date: 01/26/2009
Final Report Submission: 06/26/2011

All the best,

Christine Miller

Christine Miller, PharmD
Sr. VP, Drug Development
Sirion Therapeutics, Inc. - www.siriontherapeutics.com
P: 813.496.7325 ext 236
F: 813.496.7328
E: cmiller@siriontherapeutics.com
9314 E. Broadway Avenue
Tampa, FL 33619-7706

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From: Dean, Jane
Sent: Thursday, May 01, 2008 1:55 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - request for submission of Pediatric Plan

Importance: High

Hi, Christine,

Before we can take a final action on the NDA, we will need from you a Pediatric Plan. Could you please submit your Pediatric Plan for deferred studies to the NDA as soon as possible? A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics and/or pharmacodynamics, safety, efficacy) that you plan to conduct. The plan should also address the development of an age-appropriate formulation (if necessary). Following is a summary of information needed at this time:

Drug Information (route of administration, formulation, dosage, regimen)

Type of studies/Study Design

Age group and population in which study will be performed (list age group and population exactly as it is in the plan)

Number of patients to be studied or power of study to be achieved

Timeframe for submitting reports of studies

I hope this summary will help.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202

Fax: 301-796-9881

Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

Jane Dean

6/4/2008 02:54:48 PM

CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 5, 2008

TO: Jane Dean, Regulatory Project Manager
Sonal Wadhwa, Medical Officer

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-212

APPLICANT: Sirion Therapeutics, Inc.

DRUG: Difluprednate ophthalmic emulsion, 0.05% (Durezol)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review

INDICATIONS: Treatment of pain and inflammation following ocular surgery

CONSULTATION REQUEST DATE: January 30, 2008

DIVISION ACTION GOAL DATE: May 26, 2008

PDUFA DATE: June 26, 2008

I. BACKGROUND

Post-surgical ocular inflammation and the study drug

Corticosteroid is the mainstay of treatment for ocular inflammatory disease. Topical ophthalmic solutions are indicated for inflammation following intraocular surgery and are particularly effective for anterior chamber inflammation. Intraocular inflammation following surgery typically consists of mild, self-limited iritis with increased cells and protein in the anterior chamber. The use of anti-inflammatory agents immediately following surgery facilitates more rapid resolution of inflammation with fewer symptoms and improved patient comfort. Untreated inflammation may interfere with the patient's visual rehabilitation or lead to complications with significant morbidity, and control of post-surgical ocular inflammation is regarded as a priority in patient care.

Difluprednate ophthalmic emulsion 0.05% (ST-601) is a novel prednisolone derivative classified as a strong steroid. Currently used strong steroids (prednisolone, dexamethasone) are associated with significant adverse effects, most notably increased intraocular pressure. The availability of a strong steroid with reduced incidence of increased intraocular pressure would be an advantage in the treatment of post-surgical ocular inflammation.

Phase 3 study protocols and summary of study results

The phase 3 drug development program consisted of two phase 3 studies (ST-601A-002a, ST-601A-002b) of identical study design. The primary objective was to assess the efficacy and safety of ST-601 compared to placebo for the treatment of inflammation and pain following ocular surgery. Eligibility criteria included unilateral ocular surgery on the day before study enrollment and anterior chamber cell grade > 2 on the day after surgery. Subjects were randomized to 1 of 4 treatment arms: one drop of either difluprednate or placebo, either twice a day (BID) or four times a day (QID). Major efficacy endpoints included assessments of cell grade, cell count, and flare in the anterior chamber, ocular pain, photophobia, chemosis, bulbar injection, ciliary injection, corneal edema, and keratic precipitates. The primary efficacy endpoint was the difference in the proportions of subjects with an anterior chamber cell grade of 0 on Day 8 between the difluprednate QID group and the placebo group.

Results from the two phase 3 studies indicate that topical difluprednate therapy following ocular surgery (either BID or QID) is effective in clearing anterior inflammation (as evidenced by the primary endpoint, proportion of subjects with an anterior chamber cell grade of 0 on Day 8) and the clearing achieved on Day 8 is sustainable with either dosing regimen through Day 29 (end of treatment tapering). The proportions of subjects free of pain and/or photophobia were statistically greater with difluprednate therapy than with placebo. The incidences of adverse events, including serious adverse events, were lower with difluprednate therapy than with placebo.

Site Selection and Inspectional Strategy

Two clinical sites were selected for inspection. The two sites (sites 0030 and 0034) represented 8% (2 of 26 sites) of all clinical sites participating in the phase 3 program supporting this NDA and together enrolled 22% of all subjects (96 of 440 subjects). The key features of the two sites relevant to inspection are further described below.

- Site 0030:
 - One of the high enrolling sites in both phase 3 studies
 - Site with the highest efficacy margin (study drug - placebo)
- Site 0034:
 - The highest enrolling site in both phase 3 studies
 - Site with the lowest efficacy margin (efficacy of study drug and placebo similar)

The two sites selected produced opposite extremes in site-specific efficacy results. In selecting sites for inspection, including both studies appeared not to be important; the two studies were identical in design and were conducted in parallel. Also, the close geographic proximity of the two sites facilitated inspection of both sites by the same FDA investigator, which may in turn facilitate the interpretation of inspectional findings from the two sites. The preliminary results of the inspections are summarized below.

II. INSPECTION RESULTS

	Name of CI or Sponsor City and State/Country	Protocol Site Number Subjects	Inspection Dates	Classification	
				Interim	Final
1	Steven M. Silverstein, MD Silverstein Eye Centers Kansas City, Missouri	ST - 601A - 002b site 0030 38 subjects	completed: 5/5/08 - 5/9/08	NAI	pending
2	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. Washington, Missouri	ST - 601A - 002b site 0034 58 subjects	completed: 5/12/08 - 5/16/08	NAI	pending
3	Sirion Therapeutics, Inc. Tampa, Florida	NA	scheduled: 6/9/08 - 6/12/08	pending	pending

NAI = no action indicated / no deviations from regulations; VAI = voluntary action indicated / no significant deviations from regulations; OAI = official action indicated / significant deviations from regulations; NA = not applicable

1. Steven M. Silverstein, MD (site 0030):

- Study data were acquired electronically using eCaseLink system and computer database, which also contained all primary source data for the study.
- 53 subjects were screened, of whom 44 enrolled and 38 completed the study. Complete records for 12 subjects (selected at random) were reviewed during the inspection. The records review revealed no evidence of under-reporting of adverse events or other significant deviations. Records of primary endpoint data were reviewed in all 38 subjects completing the study. The primary efficacy endpoint data were verifiable in all subjects. No major non-compliance was noted and no FDA 483 was issued.
- Inspectional observations discussed with Dr. Silverstein included: (1) lack of assurance of correct storage conditions (including protocol-specified temperature range) in storing the test article, (2) the need to develop systems and procedures to

avoid data entry errors, and (3) the need to document adequate training in data acquisition for all employees acquiring study data using the eCaseLink system.

Recommendation: Data from this site are reliable.

2. Michael S. Korenfeld, MD (site 0034):

- Study data were acquired electronically using eCaseLink system and computer database, which also contained all primary source data for the study.
- 59 subjects were screened, of whom 58 enrolled and 52 completed the study. Complete records for 12 subjects (selected at random) were reviewed during the inspection. The records review revealed no evidence of under-reporting of adverse events or other significant deviations. Records of primary endpoint data were reviewed in all 52 subjects completing the study. The primary efficacy endpoint data were verifiable in all subjects. No major non-compliance was noted and no FDA 483 was issued.
- Inspectional observations discussed with Dr. Korenfeld included: (1) lack of assurance of correct storage conditions (including protocol-specified temperature range) in storing the test article, and (2) not always reporting serious adverse events according to the protocol-specified time frame.

Recommendation: Data from this site are reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of two US clinical sites in addition to the sponsor inspection. The deficiencies noted at the two clinical sites were minor in nature and appeared to be isolated occurrences. The inspectional findings limited to a few minor, apparently isolated deficiencies support the validity of the data submitted by the sponsor under this NDA. The results of the sponsor inspection are pending; when available (and if necessary), the results will be provided as an addendum to this clinical inspection summary.

{See appended electronic signature page}

John Lee, MD
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

John Lee
6/4/2008 06:31:40 PM
MEDICAL OFFICER

Clinical Inspection Summary for NDA 22-212 (difluprednate)

MEMORANDUM

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

DATE: May 27, 2008
TO: NDA 22-212 (difluprednate)
SUBJECT: Preapproval Safety Meeting for NDA 22-212 (difluprednate ophthalmic emulsion, 0.05%)

FDA Attendees:

Division of Anti-Infective and Ophthalmology Products (DAIOP):
Wiley A. Chambers, MD, Acting Director
Jane A. Dean, RN, MSN, Regulatory Health Project Manager
Sonal Wadhwa, MD, Clinical Reviewer

Office of Safety Evaluation (OSE):
Cherye Milburn, RN, Regulatory Health Project Manager
Melissa M. Truffa, RPh, Safety Evaluator Team Leader
Ronald Wassel, PharmD, Safety Evaluator

Background: NDA 22-212 was submitted December 21, 2007, received December 26, 2007, and filed on February 26, 2008. It was given a Priority designation with a PDUFA Goal Date of June 26, 2008, to be signed off by the director of the Office of Antimicrobial Products. A pre-approval safety meeting took place on May 27, 2008.

Summary: Dr. Chambers apprised the OSE attendees that the product being discussed was a steroid and that it had the same properties as other steroids. Therefore, it would be labeled similar to other ophthalmic steroids. OSE concurred and there were no further issues.

cc:
Archival NDA 22-212
HFD-520/Div. Files
HFD-520/Reviewers and Team Leaders

Drafted by: Jad/5-28-08
Initialed by: Mdp/6-2-08
Filename: \\cdsnas\daaodps1\Dean\NDAs\NDA22-212\Misc\PreapprovalSafetyMemo(rev).doc

MEMORANDUM

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/s/

Jane Dean

6/3/2008 02:52:39 PM

CSO

From: Dean, Jane
Sent: Monday, June 02, 2008 2:58 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - add'l micro questions

Christine, you might still be waiting on _____ for this information but if it was submitted in one of the amendments, could you please let us know where to find it?

Provide the test parameters and results for _____

Thanks.

Jane

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/s/

Jane Dean
6/2/2008 03:01:13 PM
CSO

From: Dean, Jane
Sent: Friday, May 30, 2008 11:58 AM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - loose ends

Hi, Christine - our CMC reviewer would like to tie up a few "loose ends" for his review. They are as follows:

Referenced in your 5/19/08 submission:

1. The release and 1-month stability data for the _____ container
2. Confirmation that subsequent stability results will be submitted upon completion.

Per email sent on 5/16/08 from Carmen DeBellas:

3. Confirmation of the specification change (referring to droplet size), i.e.

()

4. Confirmation of the change from _____
5. Confirmation of your commitment to _____

As usual, any idea of turn around time? Thanks!

Jane

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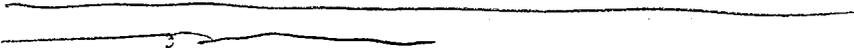
/s/

Jane Dean
5/30/2008 12:02:16 PM
CSO

From: Dean, Jane
Sent: Wednesday, May 28, 2008 1:31 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - micro IR

Importance: High

Christine, our micro reviewer has the following information request. When do you think you can provide a point by point response to these? Thanks!

1.  
2. 
3. The endotoxin specification for the drug product should be 
Please provide the test methodology and the results of  studies supporting this specification.
4. Provide the following information regarding sterilization of the tips and caps:
 - a. The name and address of the facility where sterilization will take place
 - b. Methods used for monitoring production sterilization cycles
 - c. The acceptance criteria for tips/caps sterilization cycles

Thanks,

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

Jane Dean
5/28/2008 01:44:19 PM
CSO

SIRiON

Therapeutics

May 8, 2008

Wiley Chambers, MD
Acting Director
U. S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 22-212 (0006)
Difluprednate Ophthalmic Emulsion, 0.05% (ST-601)
Clinical Information Amendment**

Dear Dr. Chambers:

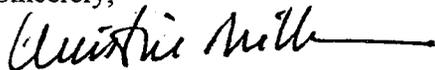
Reference is made to Sirion Therapeutics, Inc. (Sirion) New Drug Application (NDA), 22-212, submitted on December 21, 2007. Reference is also made to e-mail correspondence received by Sirion from Ms. Jane Dean, Project Manager, FDA, dated May 1, 2008, requesting that Sirion submit a Pediatric Plan.

Sirion hereby replaces our request for a waiver of pediatric studies (in Module 1) to a request for a deferral of pediatric studies as outlined in the Pediatric Plan.

A response to the aforementioned request has been provided to the Agency via e-mail to expedite the review process. By way of this amendment, Sirion hereby submits the requested information of approximately 265 KB and the corresponding updated NDA sections on a CD*. The enclosed information has been formatted to eCTD specifications and has been categorized under Module 1.11.2 "Clinical Information Amendment."

If you have any questions regarding this submission or require any additional information, please contact me directly, by telephone at (813) 496 7325 ext. 236, by email at cmiller@siriontherapeutics.com, or by fax at (813) 496-7328.

Sincerely,



Christine Miller, PharmD
Sr. VP, Drug Development
Sirion Therapeutics, Inc.

* Sirion certifies that the files on the CD are virus free and have been scanned with TREND MICRO™ Client/Server Security Agent Version 7.6.1161.

3 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

2

From: Dean, Jane
Sent: Tuesday, May 06, 2008 2:56 PM
To: 'Christine Miller'
Subject: Christine - need another analysis done! Open this

Importance: High

Could you have the sponsor do the following analysis: Number of patients in all studies with a rise in ~~_____~~ from baseline. Their current analysis is with number of patients with a rise in ~~_____~~ from baseline **and** observed ~~_____~~ →

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/s/

Jane Dean
5/7/2008 05:02:14 PM
CSO

From: Dean, Jane
Sent: Monday, May 05, 2008 12:45 PM
To: Christine Miller
Subject: FW: NDA 22-212 (difluprednate)

Please refer to your Amendment of 4/25/08.

1. Your proposal for the Average Emulsion Particle Size acceptance criteria is not acceptable. Please propose a specification that has acceptance criteria for _____
2. Your proposal for an Endotoxin acceptance criterion of _____ is not acceptable. Please propose an acceptance criterion of NMT < >
3. We note that the acceptance criteria for _____ in the drug substance are now as follows.

< >

We agree that, following the recommendations of ICH Q3A, these impurities in the drug substance do not need to be toxicologically qualified.

However, the corresponding shelf life acceptance criteria for these impurities in the drug product are as follows:

< >

ICH Q3B recommends a qualification threshold of 1.0% Please either _____

4. You describe the various container labels (1.14.1.1). Please confirm that the oval bottle is the container that will be used for the marketed commercial product and supply copies of the carton labels for these bottles. Please also confirm that these oval bottles will have a two piece label as shown (1.14.1.1.3 and 1.14.1.1.4) rather than a one piece label (e.g., as 1.14.1.1.1).
5. _____

< >

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/s/

Jane Dean
5/7/2008 04:59:22 PM
CSO



Internal Consult

Pre-decisional Agency Information

To: Jane Dean, RN, MSN
Project Manager
Division of Anti-Infective and Ophthalmology Products (DAIOP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: May 6, 2008

Re: NDA 22-212, Difluprednate Ophthalmic Emulsion, 0.05%
Labeling Review

Thank you for forwarding this consult request, dated January 25, 2008, to DDMAC. We have reviewed the draft package insert, as well as the draft carton and container labels, dated December 21, 2007, and have the following comments. We have also taken into consideration the labeling of Vexol 1% (rimexolone ophthalmic suspension), Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%), and Xibrom (bromfenac ophthalmic solution) 0.09%.

Package Insert

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

4 Page(s) Withheld

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X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3

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/s/

Lynn Panholzer
5/6/2008 11:30:48 AM
DDMAC REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-212 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Durezol
Established Name: difluprednate ophthalmic emulsion
Strengths: 0.05%

Applicant: Sirion Therapeutics
Agent for Applicant (if applicable): n/a

Date of Application: December 21, 2007
Date of Receipt: December 26, 2007
Date clock started after UN: n/a
Date of Filing Meeting: January 18, 2008
Filing Date: February 24, 2008
Action Goal Date (optional): May 29, 2008 User Fee Goal Date: June 26, 2008

Indication(s) requested: Treatment of pain and inflammation following ocular surgery

Type of Original NDA: (b)(1) (b)(2)
 AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
 Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

Version: 6/14/2006

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes

- List referenced IND numbers: 75,713

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 9/24/07 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 18, 2008

NDA #: 22-212

DRUG NAMES: Difluprednate Ophthalmic Emulsion, 0.05%

APPLICANT: Sirion Therapeutics

BACKGROUND: This drug product is a new molecular entity with an indication for the treatment of pain and inflammation following ocular surgery. The original Investigational New Drug application was submitted on November 9, 2006. An End-of-Phase 2 meeting took place on October 4, 2006 and a pre-NDA telecon on September 24, 2007.

ATTENDEES: Bergman, Boyd, Chambers, Chen, Kadoori, Langille, Lloyd, Lunn, Nevitt, Schmidt

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Wadhwa
Secondary Medical:	
Statistical:	Kadoori
Pharmacology:	Chen, Conrad
Statistical Pharmacology:	
Chemistry:	Lunn
Environmental Assessment (if needed):	
Biopharmaceutical:	Bergman
Microbiology, sterility:	Langille
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	
OPS:	
Regulatory Project Management:	Dean
Other Consults:	DMETS, DDMAC, DSI

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known 5/29/08 NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
STATISTICS	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
BIOPHARMACEUTICS			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
• Biopharm. study site audits(s) needed?								
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
• GLP audit needed?								
CHEMISTRY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Establishment(s) ready for inspection?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Sterile product?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• If yes, was microbiology consulted for validation of sterilization?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- Convey document filing issues/no filing issues to applicant by Day 74.

Jane A. Dean, RN, MSN
Regulatory Project Manager
Version 6/14/2006

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/s/

Jane Dean
4/25/2008 12:09:54 PM
CSO

From: Dean, Jane
Sent: Monday, April 14, 2008 12:20 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - IR request (micro)

Importance: High

Hi, Christine - we have another information request that needs a fairly rapid turn around time since the clock is running out. Can you give me an estimate of when a response would be possible? Thanks so much!

Jane

1. Provide the results of





2. With regard to sterilization of the  , please provide:





- 3.





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/s/

Jane Dean
4/14/2008 12:30:41 PM
CSO

From: Dean, Jane
Sent: Tuesday, April 08, 2008 10:13 AM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - IR

Importance: High

Hi, Christine - we have the following information request and was wondering what your turn around time can be on it? Thanks! Jane

Please test the registration batches (06806C, 06806D, and 06806E) for sterility after 12 months on stability at 25 deg C/40% RH.

Please provide a justification for _____ Are test batches containing _____ of the specified amount of sorbic acid adequately preserved?

Please supply the impurity profiles for the drug substance and/or product, as available, used in the following studies:

1. Four week ocular toxicity study in rabbits (Study no. SBL50-48, Lot No. 7R18)
2. Four week ocular toxicity study in dogs (Study no. SBL51-95, Lot no. GO38-01)
3. Two week ocular irritation study in rabbits using heat-degraded difluprednate (Study no. SBL41-75)
4. All clinical trials described in this NDA

We note that degraded product was used in study SBL41-75. Please supply the impurity profile for this material after degradation, if available.

Please indicate how the specified impurities _____ (described in the Amendment of 3/18/08) are toxicologically qualified.

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/s/

Jane Dean
4/8/2008 10:18:02 AM
CSO

From: Dean, Jane
Sent: Monday, March 24, 2008 4:44 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - IR (micro sterility)

Hi, Christine - our micro (sterility) reviewer has a couple of information requests he is working on. I asked him to give me what he has so far so that you all can start putting a response together. Probably in about one week, the rest of the IR will come.

Please provide the following product quality microbiology information for NDA 22-212:

1. The validation test methodology and results for the sterilizing filters.
2. The results of container closure integrity testing for the 5.0 mL
3. An endotoxin specification and stability commitment for the finished drug product, the method of endotoxin testing, and the results of the endotoxin test method validation.
4. The results of antimicrobial effectiveness testing on the finished drug product.
5. The method of sterilization for dropper tips and caps used for the 5 mL and the results of sterilization validation studies.

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

Jane Dean
3/24/2008 04:52:22 PM
CSO

From: Dean, Jane
Sent: Friday, March 21, 2008 3:58 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - Info Request (stats)

Hi, Christine - our stats reviewer has the following information request. Could you please let us know what the turn around time will be for providing this info? Thanks!

Please address the following points regarding the datasets provided:

1. In the AVI.xpt dataset, there are several missing variable values for patients in the placebo arms.
2. The provided SAS programs make reference to analysis datasets (e.g. "eff" and "subinfo") which could not be located in the submission.

Jane

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/s/

Jane Dean
3/21/2008 04:19:59 PM
CSO

From: Dean, Jane
Sent: Thursday, March 06, 2008 3:18 PM
To: 'Christine Miller'
Subject: NDA 22-212 (difluprednate) - information request
Importance: High

Christine, we have the following information request:

Please submit complete validation and bioanalytical reports for the HPLC assay used to measure 6 α ,9-difluoroprednisolone 17-butyrate (DFB) in Study 9.

Could you please let me know what you think your turn around time can be? Of course, we will always accept responses sooner rather than later, especially with this being on the shorter timeline!

Thanks!!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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/s/

Jane Dean
3/6/2008 03:28:51 PM
CSO

From: Dean, Jane
Sent: Tuesday, February 26, 2008 5:28 PM
To: 'Christine Miller'
Cc: Lunn, George; Wadhwa, Sonal; Boyd, William M; Chambers, Wiley A
Subject: NDA 22-212 (difluprednate) - CMC clarifications

Christine, below are the clarifications you have asked for in response to our 2/8/08 emailed information request. If you have any further questions after receiving today's email, please let me know asap so they can be handled as efficiently as possible.

Jane

Question 1: (Original CMC comment sent as information request in email dated 2/8/08): Validate the analytical methods used to assess _____
_____ Validation should be performed as recommended in ICH Q2(R1).

Sponsor request for clarification in email dated 2/12/08: We are currently planning a

4
2

CMC Clarification (provided in email 2/26/08): Depending on the details of the validation performed by the DMF holder and on the details of the _____ protocol this may be acceptable. However, the original HPLC method is described in DMF _____. Because of confidentiality considerations we are unable to comment to you on the adequacy of the validation of the HPLC method described in DMF _____. You should either obtain the relevant data from the DMF holder and submit it as an amendment to the NDA together with the results of a _____ study or perform a full validation as recommended by ICH Q2(R1) in your own laboratory. We remind you that this is a priority application so you should provide a timely response. Validation details should have been submitted with the original NDA.

Question 9: (Original CMC comment sent as information request in email dated 2/8/08): Validate the analytical methods in the laboratory in which the methods will be used. Validation should be performed as recommended in ICH Q2(R1). Note that when the solution stability is evaluated, a definitive statement should be made concerning the time for which the solutions are stable under specified conditions. For example, "Store solutions at [conditions] and discard after [?] hours." Do not merely report the results of experiments.

Sponsor request for clarification in email dated 2/12/08:

[]

CMC Clarification (provided in email 2/26/08): _____ would have been adequate had the _____ been satisfactory. However, there are a number of deficiencies in the original _____ reports. Specifically:

- []
 - []
 - []
- []
- []

You could address these deficiencies or perform a full validation in your laboratory as recommended by ICH Q2(R1).

Question 13: (Original CMC comment sent as information request in email dated 2/8/08):

[]

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/s/

Jane Dean
2/26/2008 05:40:40 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-212

Sirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Senior VP of Drug Development
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Difluprednate Ophthalmic Emulsion, 0.05%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is June 26, 2008.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on division workload and other potential review issues (e.g., the need for submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. In addition, we plan to initiate labeling discussions and, if necessary, communicate any postmarketing commitment requests by June 1, 2008.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

NDA 22-212

Page 2 of 2

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 19 years of age.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
2/22/2008 05:19:06 PM

From: Dean, Jane
Sent: Friday, February 08, 2008 5:52 PM
To: 'Christine Miller'
Subject: NDA 22-212 Information Request

Hi, Christine - I wanted you to get this as soon as possible. Below is a list of additional information we need from you. Could you please let me know approximately what your turn around time can be on these? That would be tremendously helpful. Also, if you have any questions or concerns, please call me directly at _____

Jane

1. Validate the analytical methods used to assess _____
_____ Validation should be performed as recommended in ICH Q2(R1). _____
2. We note (P.2.6.2) ' _____
C _____
3. Clarify the name and address of the supplier of the tip and cap assembly. Are these items covered by a DMF?
4. Because the eye is a sensitive organ please _____ the unspecified impurities limit to NMT _____ Compounds that are found above this level should be added to the specification. Compounds found at or above 1.0% should be identified and toxicologically qualified as recommended in ICH Q3B(R). DFB is the active metabolite and therefore does not need to be qualified.
5. Consider _____ the Total Impurities acceptance criterion to a value that is supported by the data in P.5.6, perhaps NMT ' _____
6. The average emulsion particle size may not adequately characterize the emulsion. Propose a _____ point specification to provide more control.
7. Add any leachables found above _____ to the drug product specification.
8. Modify the Description acceptance criterion to include _____
9. Validate the analytical methods in the laboratory in which the methods will be used. Validation should be performed as recommended in ICH Q2(R1). Note that when the solution stability is evaluated, a definitive statement should be made concerning the time for which the solutions are stable under specified conditions.

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/s/

Jane Dean

2/8/2008 05:57:52 PM

CSO

MEMORANDUM



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

DATE: January 30, 2008
TO: DFS File
FROM: Stephen E. Langille, Ph.D.
THROUGH: James McVey – Team Leader
cc: Jane Dean – Regulatory Project Manager and
George Lunn – Chemistry Reviewer
SUBJECT: NDA 22-212

On December 21-2007, Sirion Therapeutics submitted NDA 22-212 for DUREZOL (difluprednate) emulsion. DUREZOL is a topical emulsion for the treatment of pain and inflammation following ocular surgery. According to section 3.2.P.5.1 “Specifications” and section 3.2.P.8-8 “Stability” the drug product will _____

_____ The medical review division recommends that an endotoxin specification be provided for topical ophthalmics to prevent localized inflammation at the point of use. This is especially important in post-surgical topical ophthalmics which access the inner eye. Therefore, the following information request should be conveyed to the applicant:

“Provide an endotoxin specification and test method for Difluprednate Ophthalmic Solution. Please note that the acceptance criterion should apply to both product release and shelf life testing.”

END

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/s/

Stephen Langille
1/30/2008 01:28:18 PM
MICROBIOLOGIST

James McVey
1/30/2008 02:30:19 PM
MICROBIOLOGIST

DSI CONSULT: Request for Clinical Inspections

Date: January 30, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Dan-My Chu, HFD-47

Through: Joseph Salewski, Acting Director
Division of Scientific Investigations, HFD-45

From: Jane A. Dean, RN, MSN, Project Manager
William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

Subject: Request for Clinical Site Inspections

General Information

Application#: NDA 22-212

Sponsor/Sponsor contact information (to include phone/email):

Sirion Therapeutics, Inc.

Christine Miller, PharmD, 813-496-7325, —

cmiller@siriontherapeutics.com

Drug: difluprednate ophthalmic emulsion, 0.05%

Trade Name: Durezol (proposed trade name)

NME: Yes

Standard or Priority: Priority

Proposed indication: Treatment of pain and inflammation following ocular surgery

PDUFA: 6/26/08

Action Goal Date: 5/26/08

Inspection Summary Goal Date: 4/30/08

Protocol/Site Identification

Routine inspections of the clinical sites involved in this NDA are requested. See Attachment.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
DSI choice	Study ST-601A-002a		Treatment of pain and inflammation following ocular surgery
	Study ST-601A-002b		

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine inspections

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by April 28, 2008. We intend to issue an action letter on this application by May 26, 2008. The PDUFA due date for this application is **June 26, 2008**.

Should you require any additional information, please contact Jane A. Dean, RN, MSN at _____ or Sonal Wadhwa, MD at _____.

Additional Information:

This is a new molecular entity and will be DAIOP's pilot application for the new GRMP initiative.

A copy of the application is located in the electronic document room. The clinical portion of the application has been preliminarily reviewed and no issues have been identified to date to suggest a problem with data integrity.

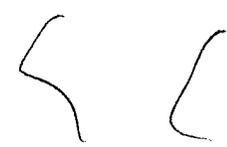
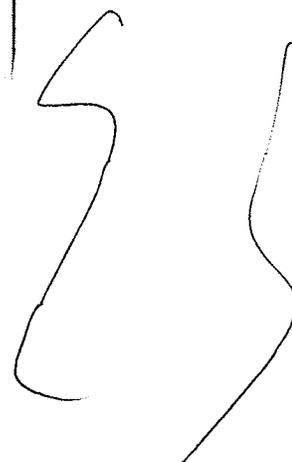
Note that the highest enroller in Study ST-601A-002a is Charles Kirby, who enrolled 36 subjects.

Note that the highest enroller in Study ST-601A-002b is Michael Korenfeld, who enrolled 58 subjects.

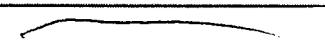
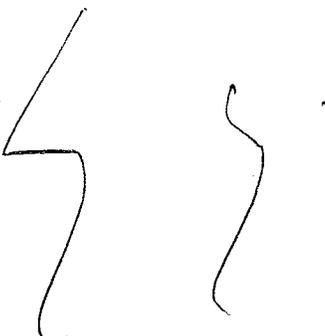
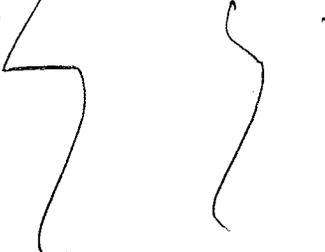
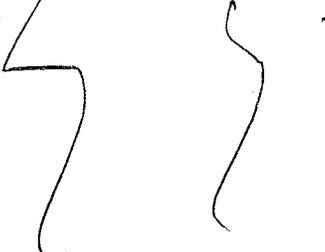
Request for Clinical Inspections

NDA 22-212 (difluprednate)

Page 3 of 6

Study No. ST-601A-002a <i>A Phase 3 Multicenter, Randomized, Double Masked, Placebo-Controlled Study of the Safety and Efficacy of Difluprednate in the Treatment of Inflammation Following Ocular Surgery</i>			
Principal Investigator Name, Title, & Organization	Site No.	Sub-Investigator(s)	Total Randomized
Carlos Buznego, MD Center For Excellence in Eye Care 8940 N. Kendall Drive, Suite 400-E Miami, FL 33176	0021		29
G. Richard Cohen, MD Cohen Laser and Vision Center 3020 N. Military Trail, Suite 150 Boca Raton, FL 33431	0032	NA	9
George Fournier, MD 2466 E. Commercial Blvd #102 Ft. Lauderdale, FL 33308	0050	NA	2
Robert DaVanzo, MD¹ Cornerstone Eye Care 307 Lindsay Street High Point, NC 27262	0054		34
Harvey B. DuBiner, MD¹ Eye Care Centers Management, Inc. Clayton Eye Center 1000 Corporate Center Dr., Suite 100, 200 Morrow, GA 30260	0049		9
Ronald E. P. Frenkel, MD 509 SE Riverside Drive, Suite 302 Stuart, FL 34994	0039	NA	2
Charles A. Garcia, MD Charles A. Garcia, MD & Associates 1315 St. Joseph Parkway, Suite 1205 Houston, TX 77002	0033		11

Request for Clinical Inspections
 NDA 22-212 (difluprednate)
 Page 4 of 6

Barrett R. Ginsberg, MD² Eye Centers of Florida 4101 Evans Ave. Ft. Myers, FL 33901	0031		0
Richard E. Hector, MD The Eye Associates 6002 Pointe West Blvd Bradenton, FL 34209	0024		1
Gregory L. Henderson, MD 403 Vonderburg Dr., Suite 101 Brandon, FL 33511	0025		18
Principal Investigator Name, Title, & Organization	Site No.	Sub-Investigator(s)	
Charles A. Kirby, MD Chattanooga Eye Institute 5715 Cornelison Rd., 6600 Bldg. Chattanooga, TN 37411	0019		36
Bernard R. Perez, MD International Eye Center 4506 Wishart Blvd. Tampa, FL 33603	0029		27
Michael H. Rotberg, MD Charlotte Eye, Ear, Nose & Throat Assoc., PA 6035 Fairview Rd. Charlotte, NC 28210	0012		28
Kenneth N. Sall, MD¹ 11423 187 th St., Suite 200 Artesia, CA 90701	0048	NA	14

¹ Investigator signed Form 1572 as a participant in identical Study ST-601A-002b, but per Statistical Analysis Plan (as a site south of the 37th parallel) the data were analyzed as a part of Study ST-601A-002a.

² No subjects were enrolled at this Investigator's site.

Study No. ST-601A-002b <i>A Phase 3 Multicenter, Randomized, Double Masked, Placebo-Controlled Study of the Safety and Efficacy of Difluprednate in the Treatment of Inflammation Following Ocular Surgery</i>			
Principal Investigator Name, Title, & Organization	Site No.	Sub-Investigator(s)	Total Randomized
Marc A. Abrams, MD PhD Abrams Eye Center 2322 East 22 nd Street, Suite 102 Cleveland, OH 4115-3176	0018	NA	1
Jeffrey A. Boomer, MD Hunkeler Eye Institute 7950 College Blvd. Overland Park, KS 66210	0020		1
David L. Cooke, MD Great Lakes Eye Care 2848 Niles Road St. Joseph, MI, 49085	0023		53
Y. Ralph Chu 7760 France Ave. S., Suite 140 Edina, MN 55435	0022		14
John C. Galanis, MD Southwest Eye Center 7331 Watson Road St. Louis, MO 63119	0056		10
David W. Karp, MD Koby Karp Doctors Eye Institute 4004 Dupont Circle Louisville, KY 4207	0026		3
Michael S. Korenfeld, MD ¹ Comprehensive Eye Care, Ltd. 901 E. Third St. Washington, MO 63090	0034		58
Howard S. Lazarus, MD John-Kenyon American Eye Institute 519 State Street New Albany, IN 47150	0009		4
Parag A. Majmudar, MD Chicago Cornea Consultants 1585 N. Barrington Road, Suite #502 Hoffman Estates, IL 60194	0027		18

Request for Clinical Inspections

NDA 22-212 (difluprednate)

Page 6 of 6

Principal Investigator Name, Title, & Organization	Site No.	Sub-Investigator(s)	
Matthew D. Paul, MD¹ Danbury Eye Physicians & Surgeons, OC 69 Sand Pit Rd., Suite 101 Danbury, CT 06810	0028		0
Steven M. Silverstein, MD Silverstein Eye Centers 4240 Blue Ridge Blvd., Suite 1000 Kansas City, MO 64133	0030		38
Timothy A. Walline, MD Eye Foundation of Kansas City 2300 Holmes Kansas City, MO 64108	0002		20

¹ Investigator signed Form 1572 as a participant in identical Study ST-601A-002a, but per Statistical Analysis Plan (as a site north of the 37th parallel) the data were analyzed as a part of Study ST-601A-002b.

² No subjects were enrolled at this Investigator's site.

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/s/

Jane Dean

1/30/2008 10:43:35 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): CDER OSE CONSULTS		FROM: Jane A. Dean, RN, MSN, Project Manager, x61202, DAIOP, OAP		
DATE 1/25/08	IND NO.	NDA NO. 22-212	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT December 26, 2007
NAME OF DRUG Difluprednate ophthalmic emulsion, 0.05%		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Ophthalmic	DESIRED COMPLETION DATE 4/25/08
NAME OF FIRM: Sirion Therapeutics				
REASON FOR REQUEST				
I. GENERAL				
<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): Trade name review				
II. BIOMETRICS				
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):		
III. BIOPHARMACEUTICS				
<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		
IV. DRUG EXPERIENCE				
<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		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review proposed name, Durezol, for NDA 22-212. This is under priority review with PDUFA goal date of 6/26/08.				
PLR/SPL is available in the EDR at the following link: \\CDSESUB1\EVSPROD\NDA022212\022212.ENX				
This NDA is the pilot for DAIOP for GRMP initiative and therefore, will be going to an Advisory Committee on May 29, 2008. (FYI only)				
PDUFA DATE: 6/26/08 ATTACHMENTS: none CC: Archival NDA 22-212 HFD-520/Division File HFD-520/Dean HFD-520/Reviewers and Team Leader				
NAME AND PHONE NUMBER OF REQUESTER Jane Dean, x61202 for Sonal Wadhwa, MD		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Jane Dean
1/25/2008 04:04:21 PM



NDA 22-212

NDA ACKNOWLEDGMENT

Sirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Senior VP of Drug Development
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

Dear Dr. Miller:

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

Name of Drug Product: Difluprednate Ophthalmic Emulsion, 0.05%

Date of Application: December 21, 2007

Date of Receipt: December 26, 2007

Our Reference Number: NDA 22-212

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 24, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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

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

If you have any questions, call me at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Jane Dean

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service.

Food and Drug Administration
Rockville, MD 20857

IND 75,713

Sirion Therapeutics, Inc.
Attention: Debra Gessner, MS
Vice President, Regulatory Affairs
11408 Sorrento Valley Road
San Diego, CA 92121

Dear Ms. Gessner:

Please refer to your Investigational New Drug Application (IND) file for ST-601 (difluprednate ophthalmic emulsion) 0.05%.

We also refer to the teleconference between representatives of your firm and the FDA on September 24, 2007. The purpose of the telecon was to discuss specific NDA/eCTD content and format questions pertaining to the proposed submission of an original New Drug Application (NDA) for ST-601.

The official minutes of that discussion are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, please call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

will be in the form of an electronic Common Technical Document (eCTD) with emphasis on Modules 4 and 5.

MEETING OBJECTIVES: To obtain Agency feedback and concurrence on the content and format of the proposed eCTD.

BACKGROUND

Sirion submitted an Investigational New Drug (IND) application on November 9, 2006, received on November 13, 2006. On June 29, 2007, a PreNDA meeting was requested and subsequently granted by the Division. The briefing document was submitted on August 13, 2007, received on August 14, 2007.

DISCUSSION

On September 18, 2007, the Division sent responses by email to the Sponsor's questions outlined in the meeting package. Those responses are identified as "FDA Response to Question X". Discussion taking place during the teleconference are captured in the section titled "Meeting Comments" which follows each question.

QUESTIONS

Nonclinical Data – Module 4

Sponsor Question 1: Will the proposed content and format for Module 4 of the eCTD be sufficient for filing and review of the proposed NDA?

FDA Response to Question 1: *The proposed content and format for Module 4 appears acceptable.*

Meeting Comment: No further discussion was necessary.

Clinical Data – Module 5

Sponsor Question 2: Will the proposed content and format for Module 5 of the eCTD be sufficient for filing and review of the proposed NDA?

FDA Response to Question 2:

Clinical Pharmacology Response:

The abbreviated report for Study SJ-TO-02 (Study 9) should include the pharmacokinetic data from the study, specifically DFB and cortisol blood levels following repeated ocular instillation of ST-601.

Clinical

The proposed content and format for Module 5 appears acceptable; however, all clinical studies should be submitted as full reports.

Please include copies of the Case Report Forms for all discontinued patient(s) regardless of the reason the patients were discontinued.

Meeting Comments: The Division reiterated the need for the eventual NDA submission to be complete with full reports, as outlined in the above responses.

ACTION ITEMS

Action Item	Owner	Due Date
Send teleconference minutes	FDA	October 24, 2007

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/s/

Wiley Chambers
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 75,713

Scirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Chief Operating Officer
3110 Cherry Palm Drive
Tampa, FL 33619

Dear Dr. Miller:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ST-601 (difluprednate ophthalmic emulsion) 0.05%.

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2006. The purpose of the meeting was to discuss the proposed clinical package in support of submitting an Investigational New Drug exemption (IND) for ST 601 (difluprednate ophthalmic emulsion) 0.05%.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 4, 2006
TIME: 12:05pm – 12:38pm

LOCATION: Conference Room 1415, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20903

APPLICATION (DRUG): PIND 75,713 (ST-601, difluprednate ophthalmic emulsion 0.05%)
INDICATION: For the treatment of _____ inflammation
_____ ocular surgery

SPONSOR: Scirion Therapeutics, Inc.

TYPE OF MEETING: Type C Guidance Meeting
MEETING CHAIR: Wiley Chambers, MD
MEETING RECORDER: Jane A. Dean, RN, MSN

FDA PARTICIPANTS:

Division of Anti-Infective and Ophthalmology Products

William Boyd, MD	Medical Team Leader
Wiley Chambers, MD	Deputy Director
Jane A. Dean, RN, MSN	Project Manager
Chris Khedouri, PhD	Statistics Reviewer
Lucious Lim, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Martin Nevitt, MD	Medical Reviewer
Linda Ng, PhD	Pharmaceutical Assessment Liaison
Thamban Valappil, PhD	Statistics Team Leader

EXTERNAL PARTICIPANTS:

Mr. Kazuto Masuda	Project Manager, Strategic Clinical Development, Senju
Christine Miller, PharmD	COO, Scirion Therapeutics, Inc.
Mr. Takuro Sekiya	Vice President, Business Planning, Senju
Roger Vogel, MD	Chief Medical Officer, Scirion Therapeutics, Inc.

PURPOSE OF THE MEETING: To discuss the proposed clinical package in support of submitting an Investigational New Drug application (IND) for difluprednate ophthalmic emulsion, 0.05%, for the treatment of _____ ocular inflammation.

MEETING OBJECTIVES (as outlined in the meeting package, dated September 1, 2006):

1. ~~_____~~
~~_____~~
~~_____~~
2. ~~_____~~ >
3. To obtain FDA agreement that the proposed clinical trial to evaluate difluprednate ophthalmic emulsion, 0.05%, for the treatment of postsurgical ocular inflammation would constitute an adequate and well-controlled trial in support of an NDA filing.
4. To obtain Agency feedback regarding the need for clinical data in pediatric patients for the treatment of _____ ocular inflammation.

1.0 BACKGROUND

Sirion proposes to conduct three Phase 3 clinical studies to support indications for the treatment of _____ ocular inflammation. The first trial would be a confirmatory Phase 3 multi-center, randomized double-masked, active-control trial in subjects with uveitis (either anterior uveitis or panuveitis). The second and third trials would be identical Phase 3 multi-center, randomized, double-masked, placebo-controlled trials in subjects who demonstrate ocular inflammation after undergoing unilateral intraocular surgery.

2.0 DISCUSSION

On September 28, 2006, the Division sent responses by email to the Sponsor's questions outlined in the meeting package. Those responses are identified as "**FDA Response to Question X**". On October 2, 2006, the Sponsor sent in clarifications and statements by email. Dialogue continued with the Sponsor after the Division perused the Sponsor's reply. It is captured in "**Meeting Comments on 10/4/06**" which incorporates the discussion that took place during the meeting.

2.1 Clinical

Sponsor Question 1:

FDA Response to Question 1:

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 X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 4

4.

5.

6.

Meeting Comments on 10/4/06: The Division acknowledged the response from the Sponsor _____ . No further discussion occurred.

The Division clarified that two weeks of treatment and a follow-up visit at six weeks would be sufficient to evaluate efficacy. No further discussion occurred.

The Division clarified the Sponsor's question regarding the open label safety trial, stating that treatment should not be open label, and that there should be a concurrent control group.

In response to the Sponsor's request for clarification on a noninferiority trial rather than an equivalence trial, the Division replied yes, it was acceptable to conduct a non-inferiority trial with a single sided 97.5% confidence interval. If superiority claims are contemplated by the Sponsor, appropriate tests for superiority should be included in the statistical plan. They will require replication in adequate and well controlled studies.

Comments from the Sponsor about the number of cells seen in the anterior chamber was addressed by the Division's agreement that the inclusion criteria be revised to be _____ cells in the anterior chamber in at least one eye.

When informed by the Sponsor what scale would be used, the Division had the following comment: there appears to be :

In response to the Sponsor's intent to include _____ the Division replied that stratification is recommended but not required.

The Division informed the Sponsor that it would be acceptable to use a noninferiority margin of _____

The Division reminded the Sponsor that the details about how missing data will be handled should be included in the statistical plan.

Further discussion ensued about whether or not tapering of the dosing regimen should be included in the labeling. This was brought up by the Sponsor because patients in the clinical trials would be on treatment for 14 days and then their dose tapered. The Division stated if the treatment was completed in 14 days then that is the information that

what would go in the label. The Division also added that if the Sponsor should beat the control, they would have labeling for safety and efficacy for the indication studied. If treatment needed to go beyond 14 days, the label should include additional information about follow-up as necessary.

Sponsor Question 2:

FDA Response to Question 2:

Meeting Comments on 10/4/06: The Sponsor accepted the response as presented and no further discussion occurred.

Sponsor Question 3: Would the FDA agree that the proposed clinical trial (ST-601A-002) to evaluate difluprednate ophthalmic emulsion, 0.05%, for the treatment of postsurgical ocular inflammation would constitute an adequate and well-controlled trial in support of an NDA filing?

FDA Response to Question 3: *ST-601A-002- may support the filing of an NDA for the treatment of postsurgical ocular inflammation, but decisions related to approval of an application can only be made after review of an NDA.*

See clinical comments for Question #1.

For post-cataract inflammation, at least a 1 unit or greater difference of the mean cell score during the post-operative between the placebo and study drug are recommended (based on a 0-4 grading scale for aqueous cells).

Intraocular inflammation after a surgical procedure is often self-limited. The primary endpoint is recommended to be at the exam at 7-8 days (± 1) not at the currently proposed exam at - days (± 1).

For ocular pain/discomfort you should consider adding a secondary endpoint for post-cataract pain evaluated as the difference in the percentage of patients pain-free during the post-operative period.

Meeting Comments on 10/4/06: The Division reiterated that endothelial cell counts should be performed in at least one study during the development of the drug product.

The Division stated that approximately 500 or more subjects using the test drug product should complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as the highest proposed for marketing.

Discussion continued on the subject of efficacy and the possibility of rebound. The Sponsor mentioned _____

Sponsor Question 4: _____

FDA Response to Question 4: _____

Meeting Comments on 10/4/06: The Sponsor accepted the response as presented and no further discussion occurred.

Sponsor Question 5: If the answer to Question 2 is no, is there a requirement for a certain number of children to be studied?

FDA Response to Question 5: *It is recommended that pediatric patients be enrolled in the studies. The inclusion of pediatric patients in the labeling of ocular inflammation indications is usually based on at least 10 pediatric patients below the age of 6 years successfully treated with the drug product.*

Meeting Comments on 10/4/06: It may be possible to receive a waiver of the requirement for pediatric studies, but there is no reason to purposely exclude pediatric patients from the studies proposed. The minimum age listed in labeling will be determined after review of the NDA. The Division recommended that the Sponsor attempt to include pediatric patients down to one year of age in their clinical studies.

3.0 ACTION ITEMS

Action Item	Owner	Due Date
Revise protocol to include changes discussed during meeting	Sponsor	No set timeframe
Submit the IND	Sponsor	End of October, 2006
Send meeting minutes	FDA	November 3, 2006

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/s/

Wiley Chambers

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