

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-211**

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

### **1.3.5.2 Patent Certification**

This section is not applicable because this NDA is being filed under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

## EXCLUSIVITY SUMMARY

NDA # 22-211

SUPPL #

HFD # 520

Trade Name Zirgan

Generic Name (ganciclovir ophthalmic gel) 0.15%

Applicant Name Sirion

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505b(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?

7 yrs (Orphan designation)

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 x NO

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

NDA# 19-661                      Cytovene

NDA# 21-304                      Calcyte

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.)

N/A                      YES                       NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III      THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Study #7 - Protocol Nos. 64.GV550/04.92 and 66.GV550/06.92  
Study #4 - Protocol No. 42-2.GV550/02.90  
Study #5 - Protocol Nos. 44.GV550/12.90 and 46.GV 550/07.90  
Study #6 - Protocol No.: 47.GV550/09.90

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 (Study #7)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2 (Study #4)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3 (Study #5)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4 (Study #6)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

- 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 (Study #7)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2 (Study #4)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3 (Study #5)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4 (Study #6)	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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

Investigation #1 (Study #7)  
 Investigation #2 (Study #4)  
 Investigation #3 (Study #5)  
 Investigation #4 (Study #6)

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?

The studies of this application were not carried out under an IND.

Investigation #1		!
		!
IND #	YES <input type="checkbox"/>	! NO x
		! Explain:

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

Investigation #1 (Study #7) !  
!  
YES  ! NO   
Explain: ! Explain:  
Carried out by Thea with right to  
reference by Sirion

Investigation #2 (Study #4) !  
!  
YES  ! NO   
Explain: ! Explain:  
Carried out by Thea with right to  
reference by Sirion

Investigation #3 (Study #5) !  
!  
YES  ! NO   
Explain: ! Explain:  
Carried out by Thea with right to  
reference by Sirion

Investigation #4 (Study #6) !  
!  
YES  ! NO   
Explain: ! Explain:  
Carried out by Thea with right to  
reference by Sirion

(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:

---

Reviewer completing form  
William M. Boyd  
Clinical Team Leader

Division Director Concurrence

Wiley A. Chambers, MD  
Acting Division Director, Division of Anti-Infective & Ophthalmology Products

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

---

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

---

/s/

---

LORI M GORSKI  
09/15/2009  
Original NDA exclusivity checklist

WILLIAM M BOYD  
09/15/2009

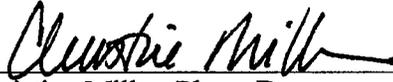
WILEY A CHAMBERS  
09/15/2009

### **1.9.1 PEDIATRIC EXEMPTION STATEMENT**

In accordance with 21 CFR 314.55(d), Ganciclovir ophthalmic gel, 0.15%, for the treatment of acute herpetic keratitis has been designated an Orphan product (Orphan drug designation # 07-2376) and therefore is exempt from pediatric use information requirements.

**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(k)(1) of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Christine Miller, PharmD  
Senior VP of Drug Development

13 May 08  
Date

**Gorski, Lori M**

---

**From:** Gorski, Lori M  
**Sent:** Friday, September 04, 2009 7:54 AM  
**To:** 'Jeremy Brace'  
**Subject:** 'US Approval 1989'

Hi Jeremy -

The statement in the label 'US Approval 1989' does refer to the June 1989 approval date of Cytovene. CFR 201.57 (a)(3) states the initial US approval of the product as an NME must be present in the label as a 4 digit year. It does not have anything to do with you cross referencing their application.

I hope this helps.

Lori Gorski  
Project Manager  
Division of Anti-Infective & Ophthalmology Products  
Phone 301-796-0722  
Fax 301-796-9881  
E-mail [lori.gorski@fda.hhs.gov](mailto:lori.gorski@fda.hhs.gov)

---

**From:** Jeremy Brace [<mailto:jbrace@siriontherapeutics.com>]  
**Sent:** Monday, August 31, 2009 4:22 PM  
**To:** Gorski, Lori M  
**Cc:** Debra Parrino  
**Subject:** RE: Word copy of the label

Hi Lori

As promised, attached is a revised version of the draft label with our comments.

As I mentioned there are just a few corrections and administrative details added. The bulk of the label is acceptable and remains unchanged.

Can you please provide one clarification on the date in the Highlights section that's states "Initial US Approval 1989". Is this correct and do we have to state it this way as I know we will get questioned as to what it means. I am assuming that this was the original date of approval for Cytovene and that this date is used because of the cross referenced route of application we have used.

Please let me know if these changes are acceptable. Comments and drafts of the packaging and labeling components will follow

Regards

Jeremy

---

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22211

-----  
ORIG-1

-----  
SIRION  
THERAPEUTICS

-----  
ZIRGAN (GANCICLOVIR  
OPHTHALMIC GEL)0.15%

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

/s/

-----  
LORI M GORSKI

09/04/2009

email regarding label comments

**Gorski, Lori M**

---

**From:** Gorski, Lori M  
**Sent:** Monday, August 31, 2009 11:03 AM  
**To:** 'Jeremy Brace'  
**Subject:** NDA 22-211 CMC issues requiring response

Hi Jeremy

Below are CMC issues to be addressed for Zirgan. It would be helpful if you could provide a timeline in which we will receive your response.

Thanks.

Lori Gorski  
Project Manager  
Division of Anti-Infective & Ophthalmology Products  
Phone 301-796-0722  
Fax 301-796-9881  
E-mail lori.gorski@fda.hhs.gov

- 1. Confusion is caused in equation 8.3 of analytical methods for the determination of ganciclovir assay and for BAC as compared to the drug product specification. This may affect the strength of the drug product. Please revise to express it as percent weight per volume. This should be consistent with the analytical method calculations, acceptance criteria in the drug product specification and labeling.**
- 2. The acceptance criterion for the particulate analysis test in the drug product specification should be modified from \_\_\_\_\_ throughout shelf life. b(4)**
- 3. The acceptance criteria for the Related Substances Assay for Unknown Individual impurity should be set at NMT  $\frac{1}{100}$ % and Total Impurities at NMT  $\frac{1}{100}$ o.**
- 3. An updated drug product specification should be submitted.**
- 4. In the Stability Protocol, a statement to inform the Review Division of failures and also to reference CFR 314.81(b)(1) for reporting to the District Office.**
- 6. An expiry dating period for 18 months will be granted.**

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

/s/  
-----

LORI M GORSKI

08/31/2009

cmc issues mailed to sponsor

**Gorski, Lori M**

---

**From:** Gorski, Lori M  
**Sent:** Thursday, August 27, 2009 11:18 AM  
**To:** 'Jeremy Brace'  
**Subject:** NDA 22-211 Carton & container comments

Hi Jeremy

After reviewing the March 9, 2009, submission the Division's preliminary carton & container comments for Zirgan are listed below.

See you tomorrow.

Lori Gorski  
Project Manager  
Division of Anti-Infective & Ophthalmology Products  
Phone 301-796-0722  
Fax 301-796-9881  
E-mail [lori.gorski@fda.hhs.gov](mailto:lori.gorski@fda.hhs.gov)

1. The purpose of the  on the proposed Zirgan carton is unclear. We recommend it be removed.
2. The storage conditions on the carton should be revised to match the draft package insert, i.e. "Store at 15°C-25°C (59°F-77°F). Do not freeze." Reference to temperature excursions should be removed.
3. We recommend the font size of the tradename and established name be increased on both the carton and immediate container labeling. Please keep the established name on the carton and container labels a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

---

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

---

/s/

---

LORI M GORSKI

08/27/2009

carton & container comments to sponsor

7/20/09

**Gorski, Lori M**

---

**From:** Jeremy Brace [jbrace@siriontherapeutics.com]  
**Sent:** Monday, July 20, 2009 9:27 PM  
**To:** Gorski, Lori M  
**Subject:** RE: Request for response - Chemistry comments for NDA 22-211

Hi Lori

Thanks for these. I will get back to you asap with timings for response

Thanks

Jeremy

---

**From:** Gorski, Lori M [mailto:Lori.Gorski@fda.hhs.gov]  
**Sent:** Monday, July 20, 2009 5:11 PM  
**To:** Jeremy Brace  
**Subject:** Request for response - Chemistry comments for NDA 22-211

Hi Jeremy,

Attached are comments from the Chemistry reviewer for NDA 22-211, Zirgan (ganciclovir ophthalmic gel) 0.15%. Please officially provide a response to the application through the electronic document room. If you have any questions please contact me.

Thanks.

Lori Gorski  
Project Manager  
Division of Anti-Infective & Ophthalmology Products  
Phone 301-796-0722  
Fax 301-796-9881  
E-mail lori.gorski@fda.hhs.gov

1. Please provide stability data on the primary batches (formula B\*) in support of proposed ~~12~~-month expiration period and storage statements. b(4)
2. Stated in various modules of the NDA submission is the quality standard is Water for injection and in other parts of the submission ~~water~~ water. Please indicate quality standard used. b(4)
3. Please provide a bacterial endotoxins acceptance criterion for the drug product.
4. Please clarify inconsistencies noted in submission for viscosity with the same nominal

7/23/2009

values (  ) in mPa's and in cPs.

**5. The structure is not correctly represented in the CMC module (3.2.S.1.2) ; double head arrow shows same structure on both sides.**

**6. No particulate analysis test is provided in the specifications. The criterion should be that the product is "free of particulate matter" through out shelf life as is appropriate. Provide a revised amended Stability Protocol and Commitment to include a test and acceptance criterion for particulate matter.**

**7. Please give rational on how determination of presence of particulate matter is otherwise monitored.**

**8. Although dosage form is a gel, ophthalmic ointments require testing to determine the presence of foreign particles and harsh or abrasive substances [211.167(b)]. No such test is proposed for the drug product specification by the contract manufacturer. Please provide assurance that the appropriate testing are performed.**

**9. It has not demonstrated that uniformity (i.e. USP <905>) is maintained to ensure that the drug substance is uniform and homogenous in the gel. A test for content uniformity may be applied**

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

/s/

-----  
Lori Gorski  
7/23/2009 08:27:05 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 22-211

**PROPRIETARY NAME REQUEST  
- CONDITIONALLY ACCEPTABLE**

Sirion Therapeutics, Inc.  
9314 East Broadway Avenue  
Tampa, Florida 33619

Attention: Jeremy Brace  
Vice President, Regulatory Affairs

Dear Mr. Brace:

Please refer to your New Drug Application dated November 14, 2008, received November 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ganciclovir Ophthalmic Gel, 0.15%.

We also refer to your March 19, 2009, correspondence, received March 20, 2009, requesting review of your proposed proprietary name, Zirgan. We have completed our review of the proposed proprietary name, Zirgan and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your March 19, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. If the NDA is not approved during this review cycle, we will re-review the name 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Darrell Jenkins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0558. For any other information regarding this application contact the Office of New Drugs (OND), Lori Gorski, Regulatory Project Manager at 301-796-0722.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

/s/

-----  
Carol Holquist  
6/2/2009 04:17:40 PM

1/23/09 DFD & Sewt

# Fax



**Division of Anti-Infective  
and Ophthalmology Products, HFD-520**  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**To:** Jeremy Brace, Sirion

**From:** Lori Gorski, Project Manager

**Fax:** 813-496-7328

**Fax:** 301-796-9881

**Phone:** 813-496-7325 ext 343

**Phone:** 301-796-0722

**Pages:** 2 (including cover page)

**Date:** January 23, 2009

**Re:** Reviewer requests for information & comments for NDA 22-211

**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Dear Mr. Brace,

Attached are the reviewer comments for ganciclovir ophthalmic gel) 0.15 % for the treatment of acute herpetic keratitis (dendritic                      ulcers). Please respond to these comments with to your application with an electronic submission to the Divison. Include NDA 22-211 on the cover page.

b(4)

Please contact me if you have any questions.

Thanks.  
Lori Gorski

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

January 23, 2009  
NDA 22-211

**NDA 22-211**  
**Original Submission**

**Submission Date:** November 14, 2008  
**Received:** November 17, 2008

**Drug:** (ganciclovir ophthalmic gel) 0.15%

**Information Request List:**

1. It would be helpful if the information you have provided for Studies 4, 5, 6 in Phase II and Study 7 in Phase III located in the M5 folder were provided as more complete data sets in a SAS format (i.e. include specific study center and country in which subjects were admitted).
2. Please submit complete bioanalytical reports for the pharmacokinetic studies submitted in the application. These reports should include assay validation results (e.g. accuracy and precision) as well as stability information for collected samples.
3. The submitted draft labeling for "Carcinogenesis, Mutagenesis, and Impairment of Fertility" and "Pregnancy Category" did not provide a comparison of animal doses with the human ocular doses in order to demonstrate margins of safety. Please use the available data to revise this portion of the label accordingly.

1/23/09



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

## FILING COMMUNICATION

NDA 22-211

Sirion Therapeutics, Inc  
Attention: Jeremy Brace  
Vice President, Regulatory Affairs  
9314 E Broadway Avenue  
Tampa, FL 33619

Dear Mr. Brace:

Please refer to your new drug application (NDA) dated November 14, 2008, received November 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ganciclovir Ophthalmic Gel 0.15%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received it in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is September 17, 2009.

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.

If you have any questions, call Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

*{See appended electronic signature page}*

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

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

/s/

-----  
Wiley Chambers  
1/23/2009 02:51:35 PM

12/19/08



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-211

**NDA ACKNOWLEDGMENT**

Sirion Therapeutics, Inc  
Attention: Jeremy Brace  
Vice President, Regulatory Affairs  
9314 E Broadway Avenue  
Tampa, FL 33619

Dear Mr. Brace:

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

Name of Drug Product: Ganciclovir Ophthalmic Gel 0.15%

Date of Application: November 14, 2008

Date of Receipt: November 17, 2008

Our Reference Number: NDA 22-211

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 January 16, 2009, 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

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

NDA 22-211

Page 2

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 Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

*{See appended electronic signature page}*

Maureen P. Dillon-Parker  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/

-----  
Maureen Dillon-Parker  
12/19/2008 08:57:51 AM  
NDA Ack Ltr

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdufa/default.htm">http://www.fda.gov/cder/pdufa/default.htm</a>					
1. APPLICANT'S NAME AND ADDRESS  SIRION THERAPEUTICS INC Christina Miller 3110 Cherry Palm Drive Suite 340 Tampa FL 33619 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  22-211	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
2. TELEPHONE NUMBER 813-496-7325 236	3. PRODUCT NAME IBD ( (Ganciclovir ophthalmic gel, 0.15%) )	6. USER FEE I.D. NUMBER PD3008043			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/82 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
<p>OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parkdawn Drive, Room 3046 Rockville, MD 20852</td> <td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parkdawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parkdawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Christina Miller</i>	TITLE <i>Sr. VP. Prog. Development</i>	DATE <i>1-29-08</i>			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$.00					
Form FDA 3397 (03/07)					

Close Print Cover sheet



Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

March 22, 2007

Sirion Therapeutics, Inc.  
3110 Cherry Palm Drive, Suite 340  
Tampa, Florida 33619

Attention: Debra Gessner  
Vice President Regulatory Affairs

Re: Designation request # 07-2376

Dear Ms. Gessner:

Reference is made to your request for orphan-drug designation submitted January 19, 2007, of ganciclovir (trade name: Virgan<sup>®</sup>) for "treatment of acute herpetic keratitis (dendritic and geographic ulcers)." Please also refer to our letter of January 24, 2007.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of ganciclovir is granted for *treatment of acute herpetic keratitis (dendritic and geographic ulcers)*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

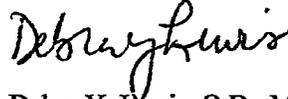
Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (see 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

Sirion Therapeutics, Inc.

2

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., RAC, at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A handwritten signature in cursive script that reads "Debra Y. Lewis".

Debra Y. Lewis, O.D., M.B.A.

Acting Director

Office of Orphan Products Development

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-211 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zirgan Established/Proper Name: (ganciclovir ophthalmic gel) Dosage Form: 0.15%		Applicant: Sirion Therapeutics, Inc Agent for Applicant (if applicable):
RPM: Lori Marie Gorski		Division: Division of Anti-Infective and Ophthalmology Drug Products
<p><b>NDAs:</b>                      NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      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><b>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.</b></p> <p style="text-align: center;"> <input checked="" type="checkbox"/> No changes                      <input type="checkbox"/> Updated                      Date of check: September 14, 2009                 </p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		September 15, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

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 <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  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: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain:	<u>Orphan designation – no PERC required</u>
❖ 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
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes
• 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

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

Answer the following questions for each paragraph IV certification:

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	x
<b>Officer/Employee List</b>	
❖ 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> )	x Included
Documentation of consent/non-consent by officers/employees	x Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	AP letter included
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	September 10, 2009
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	November 18, 2008
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<p><input type="checkbox"/> Medication Guide</p> <p><input type="checkbox"/> Patient Package Insert</p> <p><input type="checkbox"/> Instructions for Use</p> <p style="text-align: center;">x None</p>

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	none
<ul style="list-style-type: none"> <li>❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	September 10, 2009
<ul style="list-style-type: none"> <li>❖ Labeling reviews (indicate dates of reviews and meetings)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP May 28, 2009 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC August 13, 2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Review(s) (indicate date(s))</li> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> </ul> </li> </ul>	April 15, 2009 June 6, 2009
<b>Administrative/Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting) (indicate date of each review)</li> </ul>	September 1, 2009
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (signed by Division Director)</li> </ul>	x Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)</li> </ul>	x Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)</li> </ul>	x Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Postmarketing Requirement (PMR) Studies</li> </ul>	x None
<ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> </ul>	
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Postmarketing Commitment (PMC) Studies</li> </ul>	x None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located)</li> </ul>	

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

<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	included
❖ Internal memoranda, telecons, etc.	included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC</li> </ul>	x Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference</li> </ul>	September 2, 2009
<ul style="list-style-type: none"> <li>Regulatory Briefing</li> </ul>	March 27, 2009
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting</li> </ul>	May 23, 2007
<ul style="list-style-type: none"> <li>EOP2 meeting</li> </ul>	No mtg
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	N/A
❖ Advisory Committee Meeting(s)	x No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	none
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	none
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	x None
Division Director Summary Review ( <i>indicate date for each review</i> )	September 15, 2009
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	September 15, 2009
<b>Clinical Information<sup>5</sup></b>	
Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	See Cross Disciple Team Leader Review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	September 11, 2009
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	x None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	In clinical review
❖ 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 studies are > 10 yrs old
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	x None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	x Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	x None  none
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	x None requested
<b>Clinical Microbiology</b> x None	
Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	x None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) (indicate date for each review)	x None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	September 2, 2009
Statistical Team Leader Review(s) (indicate date for each review)	x None
Statistical Review(s) (indicate date for each review)	July 6, 2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	x None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	x None
Clinical Pharmacology review(s) (indicate date for each review)	June 30, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	x None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	x None
• Supervisory Review(s) (indicate date for each review)	x None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	July 8, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	x None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	x No carc
ECAC/CAC report/memo of meeting	x None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	x None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	x None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	August 31, 2009
• CMC/product quality review(s) (indicate date for each review)	August 31, 2009 September 14, 2009
• BLAs only: Facility information review(s) (indicate dates)	None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	August 5, 2009 August 21, 2009
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	<input type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	x None
❖ Environmental Assessment (check one) (original and supplemental applications)	
x Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Acceptable August 31, 2009
<input type="checkbox"/> Review & FONSI (indicate date of review)	

<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: As of August 28, 2009 <input checked="" type="checkbox"/> Acceptable
<ul style="list-style-type: none"> <li>• BLAs:           <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold