

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-810

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 50-810

Trade Name AzaSite Generic Name (azithromycin ophthalmic solution) 1% Sterile
topical ophthalmic drops

Applicant Name InSite Vision, Inc. HFD-520

Approval Date If Known April 27, 2007

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 question about the submission.

a) Is it a 505(b) (1), 505(b) (2) or efficacy supplement?
YES /XX/ NO /___/

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

505(b) (2)

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

YES /XX/ 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 /_XX_/

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

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

YES /___/ NO /_XX_/

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 /XX/

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 /XX/ NO /___/

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

NDA# 50-670

NDA#

NDA#

2. Combination product.

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

YES / / NO /XX/

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 NDA'S 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 /_XX_/

(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 /_XX_/

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 #1 003 YES /___/ NO /_ **XX**_/

Investigation #2 004 YES /___/ NO /_ **XX**_/

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 #1 003 YES /___/ NO /_ **XX**_/

Investigation #2 004 YES /___/ NO /_ **XX**_/

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 # 62,873	YES / <input checked="" type="checkbox"/> /	! NO / <input type="checkbox"/> / Explain: _____
	!	
Investigation #2	!	
IND # 62,873	YES / <input checked="" type="checkbox"/> /	! NO / <input type="checkbox"/> / 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	!	
YES / <input type="checkbox"/> / Explain _____	!	NO / <input type="checkbox"/> / Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES / <input type="checkbox"/> / Explain _____	!	NO / <input type="checkbox"/> / Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

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1.3.5.3 Exclusivity Statement

Title I of the 1984 Hatch-Waxman Amendments do not apply to drug products where the active ingredient was first approved under old section 507 of the Act. Section 125(d)(2) of the Food and Drug Administration Modernization Act of 1997 exempts "Old Antibiotics" from the exclusivity statement provisions of the Act. Since the drug product subject of this application and the Listed Drug Product (Zithromax NDA #s 50-670, 50-693, 50-710, 50-711, 50-730, 50-733, and 50-784) referenced herein meet the exemption criteria, no exclusivity statement is required

NDA 50-810 (Azithromycin 1.0% ophthalmic solution) -- InSite Vision Inc.

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 50-810 Supplement Type (e.g. SE-4, SE5): 3S Supplement Number: _____

Stamp Date: June 28, 2006 Action Date: April 27, 2007

HFD 520 Trade and generic names/dosage form: **AZASITE™** (azithromycin ophthalmic solution)
1% Sterile topical ophthalmic drops

Applicant: InSite Vision, Inc. Therapeutic Class: Ophthalmic – Antibiotic

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: AzaSite is a macrolide antibiotic indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms: CDC coryneform group G, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus mitis* group, *Streptococcus pneumoniae*

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

NDA 50-810

Page 3

cc: NDA 50-810
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG
DEVELOPMENT, HFD-960, 301-594-7337.**

CTD Module 1: Regional and Administrative Information

1.9.2 Deferral for Neonatal Study

21 CFR 314.55 requires assessment of a product in the pediatric population. In discussion with the FDA during the End of Phase 2 meeting held in January, 2003, it was agreed that the Phase 3 trials should include patients down to 1 year of age. This was incorporated into the two Phase 3 trials that were conducted and sufficient data appears to have been collected to evaluate the use of AzaSite in a pediatric population down to 1 year of age.

A subgroup of the pediatric population is the Neonatal patients at 0 to 11 months of age. This subgroup was not included in any of the clinical work that was performed. Therefore, under 21 CFR 314.55(b), InSite Vision is requesting deferred submission for this subgroup pediatric population only. InSite Vision does plan to perform further studies in order to make this product available to the Neonatal population. It is felt that more time will be needed to fully evaluate any possible safety concerns and to design a proper study for inclusion of the Neonatal population.

CTD Module 1: Regional and Administrative Information

1.12.5 Waiver Requests

Waiver for Carcinogenicity Studies

ICH Guideline S1A, 'The need for long-term rodent carcinogenicity studies of pharmaceuticals' (March, 1996) states that 'Pharmaceuticals administered by the ocular route may not need carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure.'

Data available so far indicates that there is no cause of concern for azithromycin, the active ingredient of ISV-401, of being carcinogenic. According to the latest package insert for Zithromax capsule (Pfizer Inc., 2001), azithromycin has shown no mutagenic potential according to the following genotoxicity tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. A Medline search for "azithromycin and carcinogenesis" from 1975 through 2002 failed to retrieve any paper on the subject.

The systemic exposure upon topical ocular application of 1% ISV-401 is negligible. A C_{max} of 4.4 ng/g was achieved at the 0.5-hour time-point, which rapidly decreased to approximately 1 ng/g in 2 hours (Study #I07U0301). These levels are substantially lower than 500 ng/mL, which is the level reported in humans after oral administration of a therapeutic dose of 500 mg azithromycin (Summary Basis of Approval for Zithromax[®] 1991, NDA #50-670).

Since there is no cause for concern of azithromycin, the active ingredient of ISV-401, being carcinogenic, nor is there any significant systemic exposure upon topical instillation of ISV-401, we contend that the carcinogenicity study of the ISV-401 should be waived.

This waiver request was submitted to the IND, # 62,783, serial #10, as part of the End Of Phase 2 (EOP 2) meeting. It was discussed at the EOP 2 meeting, held at FDA on January 15, 2003. It was understood at this meeting that the waiver was granted, per the meeting minutes, submitted as serial #11, on February 20, 2003.

1.12.15 WAIVER REQUEST FOR A HUMAN PHARMACOKINETICS STUDY

AzaSite™ is an ophthalmic formulation containing 1% azithromycin, a broad-spectrum antibiotic that is intended for the treatment of bacterial conjunctivitis. It is intended for dosing twice daily on the first and second day of treatment and once a day on subsequent treatment days.

We contend that it is unnecessary to perform a pharmacokinetics study in humans because, based on data from our own animal study and from the literature, the estimated blood plasma levels in humans upon ocular instillation is at least 3 orders of magnitude lower than those achieved by oral administration. Since there has been no significant systemic side effect reported during more than a decade of use of the orally administered drug in humans, the ocularly administered azithromycin (AzaSite) should be expected to cause little or no systemic side effect because of its significantly lower plasma concentrations. In addition, the plasma concentrations in humans are expected to be so low that the currently available analytical method may not be able to detect them. Based on these scenarios, a human pharmacokinetics study may not yield any meaningful information on the distribution or the systemic safety of the drug.

Azithromycin is an azalide that is structurally similar to macrolides such as erythromycin and clarithromycin. Its pharmacokinetics is characterized by rapid and extensive uptake into tissues resulting in a large volume of distribution (Vd). Both oral and intravenous administration of the drug have yielded similar Vd. Luke, et al., (1996) reported that following intravenous administration of 1 and 2 g azithromycin in normal subjects, the Vds were 30.1 L/kg and 30.5 L/kg, respectively. Azithromycin tablets and oral suspension package insert (Pfizer #70-5179-00-4) also reported the Vd to be 31.1 L/kg following oral administration.

Based on the value of Vd from these studies, we could calculate the maximum plasma concentration following ocular administration:

Volume of eyedrop = 25 uL

Concentration of azithromycin in the eyedrop = 1% = 10 mg/mL = 10 ug/uL

Assume bilateral administration;

The total amount of azithromycin administered to the eyes is

$25 \text{ uL} \times 2 \times 10 \text{ ug/uL} = 500 \text{ ug}$

Volume of distribution = 30 L/kg

Weight of a normal male subject = 70 kg

Therefore, volume of distribution of a normal subject is:

$30 \text{ L/kg} \times 70 \text{ kg} = 2100 \text{ L}$

Assume 100% absorption, the maximum plasma concentration will be:

$500 \text{ ug} / 2100 \text{ L} = 0.24 \text{ ug/L} = 0.24 \text{ ng/mL}$

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Conversely, we could estimate the plasma concentration based on our rabbit studies. In study #107U0301 (final report submitted November 1, 2001 as Serial No. 001 to this IND), following a single instillation of a 25 uL 1% AzaSite™ drop to both eyes of a rabbit, the peak plasma concentration (C_{max}) was determined to be 4.4 ng/mL. Since the blood volume of a 2 kg rabbit is about 136 mL (Kaplan and Timmons, 1979), and that of a 70 kg human is 5 L, the maximum plasma concentration in humans would be $4.4 \text{ ng/mL} \times 136 \text{ mL} / 5000 \text{ mL} = 0.12 \text{ ng/mL}$.

It is noted that this calculation does not take into account the much larger peripheral tissue compartment that humans have as compared to rabbits. Since azithromycin is known to widely distribute in tissues, the realistic azithromycin plasma concentration in humans would be much lower than 0.12 ng/mL.

Both approaches yield approximately the same maximum plasma concentrations in the sub-ng/mL range. This concentration range has not been known to cause any pharmacologic or toxicologic effects in humans. Pharmacologically, this concentration range is sub-therapeutic in its action against target bacteria. The minimum inhibitory concentrations (MICs) of azithromycin were reported to range from 0.06 ug/mL (against *Streptococcus pneumoniae*) to 4 ug/mL (*Hemophilus influenza*) (Azithromycin Package Insert, Pfizer #70-5179-00-4), which are substantially higher than the maximum attainable plasma concentrations following ocular administration. Toxicologically, this concentration range is expected to cause little, if any, systemic side effect. Oral administration of azithromycin at 500 mg/day for 3 days to healthy volunteers resulted in a peak plasma concentration of 0.42 ug/mL (Wildfeuer, et al., 1993), which is three orders of magnitude higher than the estimated azithromycin concentration upon ocular instillation. Since oral administration of azithromycin with this and other similar dosing regimens has been known to be safe for more than a decade, ocular administration of azithromycin is expected to cause little, if any, systemic side effect.

Furthermore, the estimated human plasma levels following ocular administration would be too low to be detected by currently available analytical method. A recent paper by Bahrami et al. (2005) reported a fast and sensitive HPLC method for determination of azithromycin in human serum using fluorescence detection. However, the limit of quantification of the assay was only 10 ng/mL, which is two orders of magnitude higher than the estimated blood concentrations.

In summary, based on the data from our animal pharmacokinetics studies and human systemic pharmacokinetics studies in the literature, we conclude that AzaSite™, an eyedrop formulation of azithromycin, is expected to have little systemic pharmacologic or toxicologic effects in humans. The estimated azithromycin plasma levels in humans may not be detected by the current assay methodology. Therefore, a human pharmacokinetics study employing AzaSite eyedrop formulation would be unnecessary.

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: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>INSITE VISION INC William Smith 965 Atlantic Avenue Alameda CA 94501 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>50-810</p>
<p>2. TELEPHONE NUMBER</p> <p>510-747-1225</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>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:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>AzaSite (Azithromycin ophthalmic solution 1%)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006525</p>
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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 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input 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? YES NO

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:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn 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.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE</p> <p>Sr. Manager Regulatory Affairs</p>	<p>DATE</p> <p>5/5/06</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$767,400.00

Payment ID # PD 3006525

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Thursday, April 19, 2007 7:59 AM
To: Chambers, Wiley A
Subject: FW: InSite's Responses to FDA's Responses Regarding Labeling For AzaSite 50-810
Attachments: InSite's Responses to FDA's Labeling Comments 2007-04-18.doc; Stability Data at 25 C 50-810.pdf; End of Phase 2 Mtg Minutes.pdf

Wiley - please let me know if you want me to schedule a t-con to finalize InSite's labeling. Thanks.

From: Ronald Carlson [mailto:RCarlson@insite.com]
Sent: Wednesday, April 18, 2007 4:38 PM
To: Chambers, Wiley A
Cc: Rodriguez, Raphael R
Subject: InSite's Responses to FDA's Responses Regarding Labeling For AzaSite 50-810

Please see attached Word document.

Deng, Yunfan

From: Komo, Scott
Sent: Friday, April 13, 2007 4:34 PM
To: Chambers, Wiley A; Soreth, Janice M
Cc: Deng, Yunfan; Rodriguez, Raphael R
Subject: Proposed AzaSite Labeling

Attachments: AzaSite_Labeling_Stat_Revised.doc

Addressed in Medical Office Review

Wiley and Janice,

We have the following two comments regarding the proposed AzaSite label:

1. Reporting of the superiority study results in the clinical studies section without p-value or 95% CI.

We agree with the Sponsor's proposed label that the p-value and the 95% CI should be reported for the superiority study. According to guidance for industry "Clinical studies section of labeling for prescription drug and biological products - content and format" III C: Summarizing Study Findings part 2. Treatment Effect,

"Uncertainty of Treatment Effect: A confidence interval and a p-value provide complementary information, and both should usually be provided when describing uncertainty of the treatment effect. A confidence interval provides a better numerical description of the uncertainty of the treatment effect and provides some information about its size. A p-value better conveys the strength of the finding (i.e., how likely it is that the observed treatment effect is a chance finding). However, it is generally better not to use a p-value alone."

2. The report of the non-inferiority study in the [REDACTED]

We recommend that the efficacy results of the noninferiority study [REDACTED] because of the difficulty in interpreting the efficacy results in the noninferiority setting as discussed in the regulatory briefing. In addition, there is also a concern about the difference in dosing for the active-control study from the actual proposed dosing.

b(4)

Thanks,

Scott



AzaSite_Labeling_Stat_Revised....

From: Chambers, Wiley A
Sent: Wednesday, April 11, 2007 4:27 PM
To: Silver, Harold V; Bergman, Kimberly; Lo, Ko-yu; Ellis, Amy L; Deng, Yunfan; Boyd, William M; Chen, Zhou; Marsik, Frederic J; Ng, Linda L
Cc: Soreth, Janice M
Subject: Proposed AzaSite Labeling

Attached is the propose AzaSite Labeling. Please provide comments to me as soon as you can. Please comment even if you do not have any changes.

Thanks,

Wiley

Rodriguez, Raphael R

From: Chambers, Wiley A
Sent: Tuesday, April 17, 2007 4:38 PM
To: 'RCarlson@insite.com'
Cc: Rodriguez, Raphael R
Subject: RE: NDA 50-810 Labeling Responses

Attached are responses to explain why the changes were made to the proposed labeling.

Responses to Labeling Comments

1. On pages 1 and 2 under "Indications and Usage" as well as page 4 under "Microbiology" we noted that [REDACTED] We were wondering why? In the "End of Phase 2" meeting minutes (attached, it is the last sentence of the minutes) it stated:

b(4)

In order to have specific bacteria (e.g. chlamydia) listed in the clinical section of the labeling, a minimum of 5 cases treated with ISV-401 with an eradication rate $\geq 80\%$ must be observed".

[REDACTED] was effective in 5 of 5 cases and [REDACTED] was effective in 8 of 9 cases. Could this be added back?

b(4)

Response: *The 80% refers to clinical cure. A number of the [REDACTED] cases were clinical [REDACTED] are. Both had a clinical cure rate of less than 80%.*

b(4)

2. On page 3, section 6 under "Adverse Reactions", where we list the adverse reactions reported in less than 1% of patients, we noticed that "dry eye" was added to the list. The only list of conditions that were included here were those AE's that were greater than that which occurred in placebo, and those that were "definitely, probably, or likely" related to study drug. Can you please provide a justification as to why the Agency inserted "dry eye" into the list of AE's occurring in less than 1% of patients.

Response: *In the case of ocular events, it is not appropriate to compare to vehicle since components in the vehicle may cause ocular events such as dry eye. All ocular reactions in either the test product or the vehicle are usually included.*

3. On page 3 under "Description", we note that DuraSite® was removed in reference to the formulation. We were wondering why? Could this be added back?

Response: *All of the active and inactive ingredients in an ophthalmic formulation need to be listed on the labeling. DuraSite would not be necessarily be understood as an inactive ingredient. It is potentially acceptable to include the term DuraSite as long as the exact composition of DuraSite is defined in the labeling.*

4. On page 4 under "Microbiology" we note that CDC coryneform group G* has an asterisk. The asterisk is not defined on the bottom of that section the way it is on page 2. Is this a typographical error?

Response: *Yes, it is an omission error. The definition of the asterisk should be included.*

5/3/2007

5. In the "Microbiology" section, on page 5, the second sentence:

"However, a correlation between in in vitro systemic breakpoint and ophthalmological efficacy has not been established."

The "in" before "*in vitro*" looks like a typographical error in that it should not be there.

Response: *Yes, it is a typographical error, the first "in" should be "the."*

6. On page 5 under "Clinical Studies" we note that reference to the pivotal trials being 5 days in length was deleted. This could mislead the reader into assuming that the trial was 7 days as this is the dosing that is being approved. Could a reference to the trial being 5 days be re-inserted?

Response: *The trials are not actually 5 days in length. The summary of the trial is written to convey the measurable efficacy of the product, not the expected dosing regimen. Ophthalmic anti-infectives shorten the duration of the disease. Five days of dosing is permitted because it gives the best chance of demonstrating a difference. It is important that patients continue to dose for a full course of therapy (7 days) when not in a clinical trial with careful monitoring.*

7. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that reference to the physician sample being stored at room temperature for up to 6 months was deleted. Should a separate package insert be provided for the physician sample that is identical to the commercial sample but with the different storage conditions be provided?

Response: *Physician samples are supposed to provide a method for the patient to start a medication early before being able to fill the prescription, but should be administered, stored and used in the same fashion as the trade product. Only the trade product is identified in physician labeling. There is no reason why the physician sample could not be stored in a refrigerator.*

8. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that instruction [REDACTED] **b(4)** [REDACTED] was deleted. Shouldn't this be left in so that the patient knows that refrigeration is not required?

Response: *Refrigeration is required. Although strongly discouraged, if there is a reason to eliminate the refrigeration after opening, the product must include a method for identifying the date of opening and the new two week expiration date for the product. Instructions must be included for adding (writing) the date of opening on the carton and container.*

From: Ronald Carlson [mailto:RCarlson@insite.com]

Sent: Monday, April 16, 2007 4:55 PM

To: Rodriguez, Raphael R

Subject: Labeling Responses

Attached find:

1. summary of our comments and rationale

2. A PDF of the label you sent with suggested modifications

5/3/2007

copy of the phase 2 meeting minutes as our rationale makes a citations from them.

Lastly:

One of the privileges of a regulatory affairs professional is to have their name as the addressee on the approval letter. Please use:

InSite Vision Incorporated
Ronald H. Carlson, Ph.D.
Vice President, Regulatory Affairs and Quality
965 Atlantic Ave.
Alameda, CA 94501

APPEARS THIS WAY ON ORIGINAL

Rodriguez, Raphael R

From: Ronald Carlson [RCarlson@insite.com]
Sent: Wednesday, April 18, 2007 4:38 PM
To: Chambers, Wiley A
Cc: Rodriguez, Raphael R
Subject: InSite's Responses to FDA's Responses Regarding Labeling For AzaSite 50-810
Attachments: InSite's Responses to FDA's Labeling Comments 2007-04-18.doc; Stability Data at 25 C 50-810.pdf; End of Phase 2 Mtg Minutes.pdf

Please see attached Word document.

InSite has reviewed the 17 Feb. 2007 responses provided by the FDA regarding labeling of our AzaSite™ drug product for NDA 50-810.

InSite agrees with the Agency's comment of including "dry eye" in the list of "Adverse Redactions". We have dropped this from our list of responses.

As the agency agrees with what InSite identified as typographical errors, we have also dropped them from our list.

Based on the agency's responses to InSite's other responses, we have provided additional data and regulatory precedent to further support our rationale.

In the interest of coming to an expeditious resolution on label agreement, we request a teleconference to discuss responses that InSite has proposed at the agency's earliest convenience.

Responses to Labeling Comments

1. On pages 1 and 2 under "Indications and Usage" as well as page 4 under "Microbiology" we noted that [REDACTED] organisms were omitted. We were wondering why? In the "End of Phase 2" meeting minutes (attached, it is the last sentence of the minutes) it stated:

b(4)

In order to have specific bacteria (e.g. chlamydia) listed in the clinical section of the labeling, a minimum of 5 cases treated with ISV-401 with an eradication rate $\geq 80\%$ must be observed".

[REDACTED] was effective in 8 of 9 cases and [REDACTED] was effective in 5 of 5 cases. Could this be added back?

b(4)

FDA's Response: *The 80% refers to clinical cure. A number of the [REDACTED] cases were clinical failures. Both had a clinical cure rate of less than 80%.*

b(4)

InSite's Response: *We remain confused that what is stated in the "End of Phase 2" meeting minutes is not the correct interpretation. Is there an agency regulation, guideline, or advisory committee recommendation that can clarify this requirement?*

2. On page 3 under "Description", we note that DuraSite® was removed in reference to the formulation. We were wondering why? Could this be added back?

FDA's Response: *All of the active and inactive ingredients in an ophthalmic formulation need to be listed on the labeling. DuraSite would not be necessarily be understood as an inactive ingredient. It is potentially acceptable to include the term DuraSite as long as the exact composition of DuraSite is defined in the labeling.*

InSite's Response: *We would add the following to the description of DuraSite® to the "Description" section:*

AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 290 mOsm/kg.

3. On page 5 under "Clinical Studies" we note that reference to the pivotal trials being 5 days in length was deleted. This could mislead the reader into assuming that the trial was 7 days as this is the dosing that is being approved. Could a reference to the trial being 5 days be re-inserted?

FDA's Response: *The trials are not actually 5 days in length. The summary of the trial is written to convey the measurable efficacy of the product, not the expected dosing regimen. Ophthalmic anti-infectives shorten the duration of the disease. Five days of dosing is permitted because it gives the best chance of demonstrating a difference. It is important that patients continue to dose for a full course of therapy (7 days) when not in a clinical trial with careful monitoring.*

InSite's Response: *We agree that it is important that patients continue to dose for a full course of therapy (7 days). We also think that it is important to convey to the reader how the dosing was performed to obtain that efficacy. There is regulatory precedent for being able to cite the dosing in a clinical trial even though the course of therapy exceeds it.*

SECTION OF THE LABEL	VIGAMOX (moxifloxacin hydrochloride ophthalmic solution) 0.5% NDA 21-598/S002	ZYMAR (gatifloxacin ophthalmic solution) 0.3% NDA 21-493/S006,S007	QUIXIN (levofloxacin ophthalmic solution) 0.5% NDA 21-199/S002
DOSAGE AND ADMINISTRATION	Instill one drop in the affected eye 3 times a day for 7 days.	Days 1 and 2: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times daily. Days 3 through 7: Instill one drop up to four times daily while awake.	Days 1 and 2: Instill one drop in the affected eye(s) every 2 hours while awake up to 8 times per day. Days 3 through 7: Instill one to two drops in the affected eye(s) every 4 hours while awake up to 4 times per day.
CLINICAL STUDIES	In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX™ solution produced clinical cures on day 5-6 in 66% to 69% of	In a randomized, double-masked, multicenter clinical trial, where patients were dosed for 5 days, ZYMAR® solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin treated group versus 58% (28/48) for the placebo treated group. Microbiological outcomes for the same	In randomized, double-masked, multicenter controlled clinical trials where patients were dosed for 5 days, QUIXIN™ demonstrated clinical cures in 79% of patients treated for bacterial conjunctivitis on the final study visit day (day 6-10). Microbial outcomes for the same clinical trials demonstrated an eradication rate for presumed pathogens of

SECTION OF THE LABEL	VIGAMOX (moxifloxacin hydrochloride ophthalmic solution) 0.5% NDA 21-598/S002	ZYMAR (gatifloxacin ophthalmic solution) 0.3% NDA 21-493/S006,S007	QUIXIN (levofloxacin ophthalmic solution) 0.5% NDA 21-199/S002
	patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranges from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.	clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.	90%

A modification to what the agency proposed which includes the ~~_____~~ is as follows:

~~_____~~

b(4)

4. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that reference to the physician sample being stored at room temperature for up to 6 months was deleted. Should a separate package insert be provided for the physician sample that is identical to the commercial sample but with the different storage conditions be provided?

FDA's Response: *Physician samples are supposed to provide a method for the patient to start a medication early before being able to fill the prescription, but should be*

administered, stored and used in the same fashion as the trade product. Only the trade product is identified in physician labeling. There is no reason why the physician sample could not be stored in a refrigerator.

InSite Response: We agree not to have the physician sample storage condition on the commercial package insert. We propose that the physician sample have its own package insert that allows storage at 25 C. InSite has provided stability data that justifies storage at this condition. The stability data shown in Report Number SS401.04R (provided in the NDA amendment dated 14 Feb. 2007) demonstrated the product can be stored at 25C/20% RH for 8-12 months (attached find a PDF that shows this graphically). InSite is proposing that the physician samples be dated at manufacture of 6 months with storage at 15 - 25 C (59 - 77 F). This storage condition is required because most physician samples are transported by sales personnel to the doctor's office which makes refrigeration almost impossible. It also offers the ease of storage to the doctor as not all physicians have refrigerators. Therefore, we propose: Store at 15 - 25 C (59 - 77 F) for up to six months.

5. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that instruction "Once dispenses store at 15 - 25 C (59 - 77 F)" was deleted. Shouldn't this be left in so that the patient knows that refrigeration is not required?

FDA's Response: Refrigeration is required. Although strongly discouraged, if there is a reason to eliminate the refrigeration after opening, the product must include a method for identifying the date of opening and the new two week expiration date for the product. Instructions must be included for adding (writing) the date of opening on the carton and container.

InSite Response: We would like to propose the labeling as follows;

Store unopened bottle under refrigeration at 2C to 8C (36 to 46 F). Once the bottle is opened store at _____ for up to 14 days.
Discard after the 14 days.

b(4)

InSite has patterned the storage condition of AzaSite after Xalatan, also a refrigerated ophthalmic product. Xalatan is labeled as:

2.5 mL fill, 0.005% (50 µg/mL)

Package of 1 bottle

NDC 0013-8303-04

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to the patient, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25C (77°F) for 6 weeks.

Rodriguez, Raphael R

From: Lo, Ko-yu
Sent: Wednesday, April 18, 2007 7:19 PM
To: Rodriguez, Raphael R; Chambers, Wiley A
Cc: Lo, Ko-yu; Schmuff, Norman R
Subject: RE: Labeling Responses
Attachments: Responses to Labeling Comments (2).doc

Wiley:

Please see our comments to InSites' Labeling response, #3, 7 and 8. Please let me know your final version so that I can revise the container labels accordingly.

Thanks,

Kop-Yu

Raphael: I will be on Flexi tomorrow (Doctor appointment 11 am - 1 pm) . I can be reached at office Friday after 1 pm.

I will be in **b(6)**

From: Rodriguez, Raphael R
Sent: Tuesday, April 17, 2007 8:12 AM
To: Lo, Ko-yu; Schmuff, Norman R; Silver, Harold V; Marsik, Frederic J; Bergman, Kimberly; Bonapace, Charles; Deng, Yunfan; Komo, Scott
Subject: FW: Labeling Responses

FYI --- I will setup an internal meeting to discuss these comments.

From: Ronald Carlson [mailto:RCarlson@insite.com]
Sent: Monday, April 16, 2007 4:55 PM
To: Rodriguez, Raphael R
Subject: Labeling Responses

Attached find:

1. A summary of our comments and rationale
2. A PDF of the label you sent with suggested modifications
3. A copy of the phase 2 meeting minutes as our rationale makes a citations from them.

Lastly:

One of the privileges of a regulatory affairs professional is to have their name as the addressee on the approval letter. Please

InSite Vision Incorporated
Ronald H. Carlson, Ph.D.
Vice President, Regulatory Affairs and Quality

Responses to Labeling Comments

1. On pages 1 and 2 under "Indications and Usage" as well as page 4 under "Microbiology" we noted that [REDACTED] organisms were omitted. We were wondering why? In the "End of Phase 2" meeting minutes (attached, it is the last sentence of the minutes) it stated:

b(4)

In order to have specific bacteria (e.g. chlamydia) listed in the clinical section of the labeling, a minimum of 5 cases treated with ISV-401 with an eradication rate $\geq 80\%$ must be observed".

[REDACTED] was effective in 5 of 5 cases and [REDACTED] was effective in 8 of 9 cases. Could this be added back?

b(4)

2. On page 3, section 6 under "Adverse Reactions", where we list the adverse reactions reported in less than 1% of patients, we noticed that "dry eye" was added to the list. The only list of conditions that were included here were those AE's that were greater than that which occurred in placebo, and those that were "definitely, probably, or likely" related to study drug. Can you please provide a justification as to why the Agency inserted "dry eye" into the list of AE's occurring in less than 1% of patients.

3. On page 3 under "Description", we note that DuraSite® was removed in reference to the formulation. We were wondering why? Could this be added back?

Comment: We do not include trademark in the Description (to avoid promotion). We do not recommend "DuraSite®" be added back. In addition, the firm has deleted "DuraSite®" from their revised container labels.

4. On page 4 under "Microbiology" we note that CDC coryneform group G* has an asterisk

But the asterisk is not defined on the bottom of that section the way it is on page 2. Is this a typographical error?

5. In the "Microbiology" section, on page 5, the second sentence:

"However, a correlation between in in vitro systemic breakpoint and ophthalmological efficacy has not been established."

The "in" before "*in vitro*" looks like a typographical error in that it should not be there.

6. On page 5 under "Clinical Studies" we note that reference to the pivotal trials being 5 days in length was deleted. This could mislead the reader into assuming that the trial was 7 days as this is the dosing that is being approved. Could a reference to the trial being 5 days be re-inserted?

7. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that reference to the physician sample being stored at room temperature for up to 6 months was deleted. Should a separate package insert be provided for the physician sample that is identical to the commercial sample but with the different storage conditions be provided?

Comment: (i) The HOW SUPPLIED /STORAGE AND HANDLING Section of a commercial package insert should not contain information about physician sample. In addition, the presence of a conflicting storage condition for the physician sample (store at room temperature for up to 6 months) right under the storage/handling instruction for the commercial product (store at 2-8°C (36-46°F), after dispensing, store between 15°-25°C (59-77°F), discard unused portion 14 days after opening) will confuse patients; (ii) I am not aware there is a separate package insert for the physician sample (Wiley: Is this correct?)

8. We note that on page 6 under **HOW SUPPLIED/STORAGE AND HANDLING** that instruction [REDACTED] was deleted. Shouldn't this be left in so that the patient knows that refrigeration is not required?

Comment: Wiley: You told me that you want the firm to put a sticker with dispensing date and storage/handling conditions on the bottle. Should the information [REDACTED]

be also included in the **HOW SUPPLIED Section.**

b(4)

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Tuesday, April 17, 2007 10:19 AM
To: 'Ronald Carlson'
Subject: NDA 50-810 Labeling Responses

Thanks Ron. Please submit this officially to your NDA.

I have forwarded your labeling comments to the primary reviewers. Will setup an internal meeting to discuss and finalize your label. Hoping all will be in agreement by the end of this week.

Regards,
Raphael

From: Ronald Carlson [mailto:RCarlson@insite.com]
Sent: Monday, April 16, 2007 4:55 PM
To: Rodriguez, Raphael R
Subject: Labeling Responses

Attached find:

1. A summary of our comments and rationale
2. A PDF of the label you sent with suggested modifications
3. A copy of the phase 2 meeting minutes as our rationale makes a citations from them.

Lastly:

One of the privileges of a regulatory affairs professional is to have their name as the addressee on the approval letter. Please use:

InSite Vision Incorporated
Ronald H. Carlson, Ph.D.
Vice President, Regulatory Affairs and Quality
965 Atlantic Ave.
Alameda, CA 94501

Rodriguez, Raphael R

From: Ronald Carlson [RCarlson@insite.com]
Sent: Monday, April 16, 2007 4:55 PM
To: Rodriguez, Raphael R
Subject: Labeling Responses
Attachments: Responses to Labeling Comments.doc; Labeling With InSite's Resposes of FDA's Comments.pdf; End of Phase 2 Mtg Minutes.pdf

Attached find:

1. A summary of our comments and rationale
2. A PDF of the label you sent with suggested modifications
3. A copy of the phase 2 meeting minutes as our rationale makes a citations from them.

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InSite Vision Incorporated
Ronald H. Carlson, Ph.D.
President, Regulatory Affairs and Quality
905 Atlantic Ave.
Alameda, CA 94501

8 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Friday, April 13, 2007 3:24 PM
To: 'Ronald Carlson'; 'Anisha Wharton'
Subject: NDA 50-810 AzaSite Draft Labeling

Attachments: AzaSite_Labeling FDA Apr 12.doc

Ron & Anisha - sorry for the delay. Please find attached copy of the draft labeling from the review team. Please review each page. If you have no changes or modification please initial & date each page. In addition, the review team is recommending - revision of the carton and container labeling to match the package insert.



AzaSite_Labeling
FDA Apr 12.do...

Rodriguez, Raphael R

From: Ronald Carlson [RCarlson@insite.com]
Sent: Tuesday, April 03, 2007 12:12 PM
To: Rodriguez, Raphael R
Subject: Fwd: Review Aids for NDA 50-810 Amendment 04/02/07: Response to CMC Questions

Attachments: physician-container-desc.pdf; commercial-carton-desc.pdf; commercial-container-desc.pdf; physician-carton-desc.pdf; SS401.05P.pdf; Azithromycin Monohydrate COAs.pdf; cover.pdf



physician-container-desc.pdf (... desc.pdf (18... er-desc.pdf ... sc.pdf (181... SS401.05P.pdf (66 KB) Azithromycin Monohydrate COAs... cover.pdf (75 KB)

Here is an e-mail copy of the disk that you should receive today. The documents aren't linked here as is the disk but may help expedite your review and circulation.

>>> Michael Panos 4/3/2007 9:02:30 AM >>>

Raphael,
Submitted for your review are the 7 attachments contained in the NDA 50-810 amendment submitted on 2 April, 2007. The contents of these attachments are as follows:
Cover Letter
Physician Carton Label
Physician Container Label
Commercial Carton Label
Commercial Container Label
Stability Study Protocol for the Commercial Production Lots of 401P2100E2 Azithromycin Monohydrate Certificate of Analysis
Please let me know if you need any additional items to aid in your review.

Thank you,

Ronald Carlson, Ph.D.
Vice President of Regulatory Affairs and Quality

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Monday, April 02, 2007 2:14 PM
To: 'Ronald Carlson'; 'Anisha Wharton'
Subject: FW: AzaSite azithromicin NDA 50-810

Ron & Anisha - below are the actual comments of the CMC reviewers concurred by Dr. Chambers. Please send your responds to your IND.

In a telephone conversation on 3/29/2007 between InSite's, and FDA's Ko-yu Lo and Norman Schmuff. The only contentious item was #3 which requested a specification change for certain impurities. InSite described their newly submitted plan to have a 2.5 mL physician sample which was identical to the product proposed for market, except for a different label, indicating an expiry period of 6 months when stored at controlled room temperature. InSite suggested that this product could not meet the FDA's proposed impurity specifications, and suggested that the existing specification should stand as-is. We have considered the request, and find that InSite's specification proposal acceptable. We also find the proposal to distribute physician samples with the 6 month expiry period acceptable.

CMC LABELING COMMENTS

To avoid confusion, we recommend the deletion of information in the Storage and Handling section relating to "Physician Samples."

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Wednesday, March 28, 2007 8:06 AM
To: 'Ronald Carlson'
Cc: 'Anisha Wharton'
Subject: FW: Chemistry IR for NDA 50-810

Attachments: Chemistry comments.doc

Good morning Ron: sorry for not delivering this information requests yesterday. Please find attached IR from the chemistry group.

Please let us know the availability of your chemistry group for a quick teleconference.

Thanks,
Raphael



Chemistry
mments.doc (39 KB)

Rodriguez, Raphael R

From: Rodriguez, Raphael R
Sent: Wednesday, March 21, 2007 8:06 AM
To: 'Ronald Carlson'
Subject: NDA 50-810 Information request. Ron forwarding this request from the micro reviewer. Thanks.

Attachments: 50810 IR.doc



50810 IR.doc (32
KB)

Rodriguez, Raphael R

From: Rosario, Lilliam
Sent: Wednesday, September 27, 2006 2:19 PM
To: Rodriguez, Raphael R
Cc: Rosario, Lilliam
Subject: Azasite update

Raphael

I want to follow up on various issues for Azasite:

- Have you received a HLDE table for this application? IF so, please send link to EDR location.
- Did you receive an updated label addressing the deficiencies that were identified in our initial review (7/17/06)? If not, you may want to consider asking the Sponsor to resubmit before mid-cycle so your review team can work from the most updated version of the label.
- Have you set up labeling meetings? When you do, please send meeting invitation to SEALD@fda.hhs.gov.

Please let me know if you have further questions

Lilliam

Please note new email address: lilliam.rosario@fda.hhs.gov

Acting Team Leader

Study Endpoints and Label Development Team

DA/CDER/ONDIO

10903 New Hampshire Avenue

Building #22

Room # 6478

Silver Spring, MD 20993

Rodriguez, Raphael R

From: Lo, Ko-yu
Sent: Monday, February 05, 2007 5:21 PM
To: Rodriguez, Raphael R
Cc: Schmuff, Norman R; Ng, Linda L; Lo, Ko-yu
Subject: RE: NDA 50-810 InSite's AzaSite 1 mL Fill Free Physician Sample

Attachments: Response to [REDACTED] . physician sample.doc **b(4)**



Response to 1 mL
physician sam...

Raphael:

Please forward our response to InSite.

Thank you,

Ko-Yu

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

From: Rodriguez, Raphael R
Sent: Wednesday, January 31, 2007 11:31 AM
To: Lo, Ko-yu; Ng, Linda L; Schmuff, Norman R
Subject: NDA 50-810 InSite's AzaSite [REDACTED] Fill Free Physician Sample

b(4)

FYI - kindly answer questions below. Thanks.

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

From: Ronald Carlson [mailto:RCarlson@insite.com]
Sent: Wednesday, January 31, 2007 10:53 AM
To: Rodriguez, Raphael R
Subject: NDA 50-810 InSite's AzaSite [REDACTED] Fill Free Physician Sample

b(4)

InSite would like to receive feedback from the FDA regarding our proposal to provide physicians free samples of what will be our commercially available AzaSite eye drop product for bacterial conjunctivitis. AzaSite is a 1% solution of azithromycin. The NDA's number is 50-810 and was submitted 28 June 2006.

The commercial product is a 2.5 mL fill in a 5.0 mL container. For the free samples to provide physicians, we propose a [REDACTED] fill in this same 5.0 mL container but change the labeling to reflect that this is a free sample for the physician and not for resale.

b(4)

As this is a different fill volume but otherwise identical in the manufacturing process to the commercial product, we would perform stability studies in support of this difference.

Does the agency:

Think that there should be other studies other than stability to support this difference in fill volume?

* Have an objection to performing 25C accelerated stability for 6 months since InSite has considerable data at 5 and 25 C on the 2.5 ml

fill wile also continuing the real time 5C stability for 2 years?

* Does the agency have any advice on how to proceed with development of free physician samples?

After receiving feedback we will submit a formal proposal via an amendment to the NDA. I was hoping that some feedback before submitting the amendment would facilitate moving forward with development of the free physician sample.

Thank you,
Ron Carlson

Rodriguez, Raphael R

From: Chambers, Wiley A
Sent: Monday, October 23, 2006 8:07 AM
To: Rodriguez, Raphael R; Chambers, Wiley A
Cc: Deng, Yunfan; Valappil, Thamban
Subject: RE: Stat Comments for NDA50810

Please do not send. Yunfan should finish her review with the information submitted. The confidence intervals were agreed on in advance by the Division. The analysis should be performed as described in the protocol.

Wiley

From: Rodriguez, Raphael R
Sent: Monday, October 23, 2006 7:47 AM
To: Chambers, Wiley A
Cc: Deng, Yunfan; Valappil, Thamban
Subject: FW: Stat Comments for NDA50810

Wiley - see comments of the stat reviewer. Thanks .

From: Deng, Yunfan
Sent: Friday, October 20, 2006 12:00 PM
To: Rodriguez, Raphael R
Cc: Valappil, Thamban
Subject: Stat Comments for NDA50810

i Raphael,

Please send the following stat. comments to the sponsor ASAP.

Thanks,
Yunfan

NDA 50810

Drug Name: AzaSite™

Sponsor: InSite Vision Inc.

Indications: Treatment of Bacterial Conjunctivitis

Studies: Study C-01-401-003 (A Vehicle- Control Superiority Study), and Study C-01-401-004 (An Active-Control Non-Inferiority Study)

Statistical Comments:

We have been unable to find any discussion as to the appropriateness of the pre-specified non-inferiority margin used in your phase 3 study C-01-401-004. Please provide a justification for your choice of non-inferiority margin for the study or direct us to its location in the submission. Justification of the non-inferiority margin should be provided in terms of M1 (benefit of active drug over placebo) and M2 (acceptable loss of effect relative to control while preserving 50 % of the control drug effect). More details can be found in ICH E9 and E10 guidelines.

As discussed in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials" (located at www.fda.gov/cder/guidance/index.htm) a non-inferiority margin should be defined as "the largest difference that can be judged as being clinically acceptable

and should be smaller than differences observed in superiority trials of the active comparator.” It “cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial.” Furthermore, 21CFR314.126(b)(2)(iv) states the following:

If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

APARS THIS WAY ON ORIGINAL

driguez, Raphael R

From: Delasko, Jeanne
Sent: Wednesday, August 23, 2006 4:02 PM
To: Rodriguez, Raphael R; Burke, Laurie B
Subject: NDA50810:Azasite

- He is correct in that InSite just needs to add the cross ref. (2.1) after this statement.
- Only if manufacturers have a dedicated website for voluntary reporting of adverse reactions would they list it, in addition to the phone number. The website listing is not a requirement. [See 21 CFR 201.57(11)(iv)]. If there isn't any website, just list the phone number. Email addresses are not permitted either because they would not provide a structured format for reporting.
- He is correct in his last bullet for keeping the titles/headings also consistent in the FPI.

I don't think we need a telecon unless you do Laurie. Ralph, can you relay this information to the applicant?

From: Rodriguez, Raphael R
Sent: Wednesday, August 23, 2006 3:36 PM
To: Burke, Laurie B; Delasko, Jeanne
Subject: FW: 74 Day Letter Issues from SPL

see questions below. Thanks.

From: William Smith [mailto:WSmith@insite.com]
Sent: Wednesday, August 23, 2006 3:31 PM
To: Rodriguez, Raphael R
Cc: Lyle Bowman; Michael Panos
Subject: 74 Day Letter Issues from SPL

Raphael,
 Here are the questions that I have for Laurie Burke in the SPL group: Please see the bolded sections below.

Thanks,
 Will

If we need a telecon tomorrow morning, the dial-in number is 866-470-2925
 Conference Code: 5426381371

Highlights:

- Since there are no recent major changes, please delete this section heading. [See 21 CFR 201.56(d)(4)].
- Regarding Dosage and Administration, please include a cross-reference for your first statement (i.e., Days 1 and 2: Instill 1 drop in the affected eye(s) two times per day). [See 21 CFR 201.56(d)(3)]. **What do**

they mean by "cross-reference?" Do they want an identifying section number for example (2.1) for the days 1 and 2 statement, and a separate identifying number (2.1) for the days **■** statement? I assume that it does not refer to adding an annotation reference, so this is why I presumed that I would not need to contact Janet Norden again. Please confirm. **b(4)**

- Regarding the adverse reactions reporting statement, you list a company website. Note that a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]. **We need to know exactly what needs to be provided: An 800-number is required to be placed in the highlights section of the labeling--correct? What type of website is required? Can it be a link to our company website that provides the 800-number? Can it be a simple email "contact us" type of link that allows the person reporting an AE to fill in a blank box (also displaying the 800-number) or must it specify "AE Reporting Email?" Finally, must it be a link to our website that contains access to a blank MEDWATCH form as well as providing the 800-number? We are willing to make whatever changes are necessary once we fully understand the requirements.**
- Full Prescribing Information: Contents:
- Under Warnings and Precautions, you list full sentences to describe each subsection instead of headings. Please consider using short headings or titles. [Best Practices] **We are willing to abbreviate these statements, (except for the first one which is already brief) but then the same changes should also be made to the highlights section, and to the headings of those sections in the FPI for consistency.**
- For Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. However, the numbering does not change. It must read as follows:
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)

Please fix numbering in Contents and Full Prescribing Information for Section 8. [See 21 CFR 201.56 (d)(1)].

- Regarding Nonclinical Toxicology, 13.1 should read Carcinogenesis, Mutagenesis, Impairment of Fertility. Delete the word "and." [See 21 CFR 201.56(d)(1)].

Full Prescribing Information (FPI):

- As mentioned above, please fix numbering for Section 8 (Use in Specific Populations).
- Regarding references, is this information necessary? If not, please consider removing. [See 21 CFR 201.57(c)(16)]

William H. Smith, Ph.D.
Regulatory Affairs
InSite Vision
(510) 747-1225

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driguez, Raphael R

From: William Smith [WSmith@insite.com]
Sent: Thursday, June 01, 2006 12:32 PM
To: Rodriguez, Raphael R
Cc: Ronald Carlson
Subject: PLR: Contraindications and Safety Datasets--Revised question #2

Hello Raphael,

We have two separate and unrelated questions for the division related to AzaSite IND 62,873 and the forthcoming NDA:

1. We are finalizing the draft labeling for our azithromycin 1% ophthalmic solution NDA 50-810. After watching a webcast of "CDER Live" recently featuring John Jenkins and a panel of FDA experts on the topic of implementation of the PLR, we have a question about the presentation of contraindications.

Our current proposed wording is: [REDACTED] According to the webcast, and in accordance with the draft guidance, we would simply state under contraindications: *None*. b(4)

We have not actually observed any [REDACTED] in our clinical trials. Based on the January [REDACTED] guidance, and reinforced by the recent Webinar broadcast, if we have not actually observed a serious [REDACTED] for which the harm outweighs the potential benefit, we cannot list this as a contraindication. Can we instead place this information in the warnings and precautions section? b(4)

There is confusion because three of the four mock package inserts provided on the Agency's website follow the guidance, but one example, Fantom (motnaf) does give a contraindication of hypersensitivity to the product or one of its components.

2. We would like to know whether the Agency will accept the combined safety database in the form of a combined **ISS/ISE** database.

Thanks for your input on both issues as we work towards completing our NDA for submission in the next few weeks.

Best regards,
Will

William H. Smith, Ph.D.
Sr. Manager, Regulatory Affairs
InSite Vision
(510) 747-1225

Regulatory Briefing Agenda
February 9, 2007

Subject:	NDA 50810 Azithromycin Ophthalmic Solution		
Indication:	Treatment of bacterial conjunctivitis		
Purpose:	This meeting is to present information concerning the studies submitted in support of the NDA. The discussion is expected to involve issues related to non-inferiority, prior agency agreements, and definitions of substantial evidence.		
Meeting:	Regulatory Briefing		
Meeting Date:	February 9, 2007		
Meeting Time:	1:00 p.m. – 3:00 p.m.		
Meeting Location:	White Oak Shared Use Building Room 2046		
Chair:	John Jenkins, MD		
Facilitator:	Susie Dill		
Project Manager:	Raphael Rodriguez		
Time	Item #	Agenda Item	Presenter
5 min.	1	Opening Remarks	John Jenkins, MD
5 min.	2	Introduction	Wiley Chambers, M.D.
15 20min.	3	Presentation (clinical) (biostatistics)	Wiley Chambers, M.D. Thamban Valappil, Ph.D. Yunfan Deng, Ph.D.
70min.	4	Questions/Opinions	Panel
5min.	5	Wrap-Up	John Jenkins, MD

Regulatory Briefing - February 9, 2007
Azithromycin Gel Forming Solution for Bacterial Conjunctivitis

Issue

Acceptability of one vehicle controlled study and one active controlled study in support of a New Drug Application when it is known that the margin used for the active controlled study may overlap the confidence interval needed to differentiate the drug product and its vehicle

Disagreement between Clinical and Statistical Reviewers

The clinical and statistical reviewers disagree on whether the two studies provide adequate evidence of effectiveness. The clinical reviewers consider the two studies (one demonstration of superiority and one clinical demonstration of equivalence) to be sufficient to establish substantial evidence of effectiveness. The margin demonstrated in this case is considered sufficient in association with the impact of the antimicrobial kill on the public health impact of treating the disease and that vehicle treatment is an effective therapy. The clinical reviewers do not consider the number of patients needed to be studied to satisfy the statistical concerns in equivalence trials to be achievable. The clinical reviewers consider the population studied in vehicle controlled studies to be potentially different from the intended population for marketing and the inclusion of an active control to be more informative than a second vehicle controlled study.

Question

➤ Please offer advice?

Regulatory History

The clinical plan was discussed between the Applicant and the Agency on April 9, 2001. The Agency provided the Applicant with the following clinical trial plan. Two replicative trials showing superiority to vehicle in clinical cure rate in the per protocol analysis. Clinical cure is defined as the resolution of signs and symptoms (i.e. a score of 0) or demonstration of superiority to vehicle in one trial and equivalence to tobramycin or one of the approved fluoroquinolones in another trial. Equivalence was to be demonstrated by showing that the 95% confidence interval for the difference in success rates is within $\pm(1-p_c)$ where p_c is the clinical cure rate. If p_c is less than 80%, the CI must be within ± 0.2 . Additionally, the intent to treat analysis must show that the clinical cure rate is not inferior to vehicle.

The Applicant and the Agency agreed to the development plan on January 15, 2003, consisting of one vehicle controlled study and one equivalence study with the confidence margins listed above. This was confirmed by the Agency in a July 15, 2004, response to June 9, 2004, submission.

FDAMA**SEC. 119. CONTENT AND REVIEW OF APPLICATIONS**

505(b)(5)(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except-- (i) with the written agreement of the sponsor or applicant; or (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

No new issues identified since the start of the clinical trials

The issues involved in using an equivalence trial were known in 1988 and discussed with the Directors of the Office of Drug Evaluation I and II. Discussed with multiple applicants between 1988 and 2004. The clinical plan discussed with the Applicant is the basis of the approvals of ciprofloxacin ophthalmic solution, norfloxacin ophthalmic solution, ofloxacin ophthalmic solution, gatifloxacin ophthalmic solution, moxifloxacin ophthalmic solution and levofloxacin ophthalmic solution. The issues involved in using an equivalence trial were discussed at an Advisory Committee Meeting in 1990. The criteria listed in 505(b)(5)(B) and (C) of the Food Drug and Cosmetic Act as amended have been met with respect to accepting the parameters of the design and size of the clinical trials.

Background on Bacterial Conjunctivitis

Bacterial conjunctivitis is almost always (~95-98%) self limited lasting 10-14 days. Some bacteria may cause corneal perforations and lead to loss of sight, such as *N. gonorrhoeae*, *N. meningitides* and *P. aeruginosa*. Some bacteria may lead to chronic infections such as *Staphylococcus*. In the presence of a corneal abrasion, conjunctivitis may lead to a corneal ulcer. In standard clinical practice, anti-infective therapy is almost always proscribed if the patient is believed to have bacterial conjunctivitis and it would be considered malpractice not to treat unless there were very frequent follow-up visits. Cultures are usually taken only when antimicrobial therapy fails and it is very rare for the

combination of an anti-infective and tincture of time to be ineffective regardless of bacterial sensitivity results. The predominant safety concern is an allergic reaction due to the drug product which almost always resolves upon discontinuation of the drug product. The potential consequences of not treating a bacterial conjunctivitis are the possible risk of loss of sight, the increased chances of spreading the infection and the longer loss of school or work time while potentially infective to other individuals.

The reasons for the clinical plan that has been proposed are based on the vehicle being an active treatment in the disease, not a true placebo. The vehicle, as a multi-dose ophthalmic product is required by regulation to include an antimicrobial preservative. It is effective in killing the most common ocular bacterial, hence its use as a antimicrobial preservative. The application of a vehicle to the eye, also washes out microorganisms reducing the number of infective microorganisms from the eye. Studies demonstrating statistical exclusion of vehicle rate are not practical. The estimates of the number of patients needed per arm to demonstrate equivalence with a tight enough confidence interval to rule out the potential effectiveness of the vehicle would require 1,500 to 12,000 patients. Additionally, as expressed by potential investigators in clinical studies, institutional review boards and the Ophthalmic subcommittee of the Anti-Infective Advisory Committee, the population of patients that are studied in vehicle controlled studies are not necessarily representative of the intended population. The superiority of anti-infective ophthalmic drug products, while small, has been reproduced multiple times in adequate and well controlled studies submitted to the Agency in support of New Drug Applications.

A number of products were approved for the treatment of ocular infections based on studies which did not include comparison to the product's vehicle. These include, sulfacetamide sodium ophthalmic solution, chloramphenicol ophthalmic solution, erythromycin ophthalmic ointment, tetracycline ophthalmic ointment, bacitracin ophthalmic ointment, polymyxin B/bacitracin ophthalmic ointment, polymyxin B/neomycin/bacitracin ophthalmic ointment, polymyxin B/neomycin/gramicidin ophthalmic solution, gentamicin ophthalmic solution, tobramycin ophthalmic solution, and polymyxin B/ trimethoprim ophthalmic suspension. In 1988, NDAs were submitted for ofloxacin and norfloxacin ophthalmic solutions. These NDAs were submitted with seven day comparison to gentamicin and tobramycin ophthalmic solutions and demonstrated >90% improvement in all groups. Conjunctivitis, blepharoconjunctivitis and blepharitis combined in same study. After internal discussion within the Division of Anti-Infective Drug Products and with the Directors of the Office of Drug Evaluation I and II, approvable letters were issued requiring demonstration of superiority of the products to their vehicle or another anti-infective drug product.

Between 1988 and 1990, Ciprofloxacin ophthalmic solution, Ofloxacin ophthalmic solution and Norfloxacin ophthalmic solution were approved for the treatment of bacterial conjunctivitis after demonstrating superiority to their vehicles. Each one performing a single vehicle controlled study to support their previously conducted active controlled equivalence trials.

b(4)

b(4)

Following these approvals, in December of 1990, an Advisory Committee Meeting of the Ophthalmic Subcommittee of the Anti-Infective Advisory Committee, supplemented with additional ophthalmologists and systemic anti-infective physicians from the full committee, was called to discuss a number of issues involving the design of ophthalmic anti-infective clinical studies. The discussion included the use of microbial inclusion criteria, the separation of conjunctivitis, blephroconjunctivitis and blepharitis, the use of vehicle controlled studies, the use of microbial endpoints, and the use of cure versus improved as an endpoint. The committee recommended separation of conjunctivitis and blepharitis, the use of clinical cure as an endpoint and including one vehicle controlled study and equivalence to one active controlled study. Equivalence was defined as $\pm 10\%$ if control was $\geq 90\%$, $\pm 20\%$ if control was $\geq 80\%$ and $\pm(1-\text{control})$ if $80\% < \text{control} < 90\%$.

Between 1995-2006, gatifloxacin ophthalmic solution, moxifloxacin ophthalmic solution and levofloxacin ophthalmic solution were developed and approved. They each demonstrated superiority to vehicle in cure after 3-5 days in a single study and equivalence to Ofloxacin or Tobramycin -margin $\pm 10-20\%$ based on cure rate of control.

Against the advice of the ophthalmic clinical group, in December 2006, the Applicant for azithromycin gel forming ophthalmic solution was asked to provide a justification for their choice of non-inferiority margin for the study C-01-401-004. The Applicant responded that the study was designed in accordance with the Agency's instructions provided in the End of Phase 2 Meeting on January 15, 2003, and that they were not aware of any published placebo-controlled studies with Tobramycin in the treatment of bacterial conjunctivitis.

The ophthalmic clinical group has reviewed the literature and the past submissions of anti-infective ophthalmic products. Most of the vehicle controlled studies conducted were performed to support NDAs. Most of the results of these studies are not published in the literature and the published results do not necessarily include all details of the study. The Agency has the most complete collection of vehicle controlled studies known.

Azithromycin gel forming ophthalmic solution is submitted as a 505(b)(2) with a reference to the systemic formulation of Azithromycin and its applicable in vitro kill rates and systemic safety profile. Azithromycin is an old antibiotic and is not entitled to patent listings. If reference is made to other vehicle controlled clinical studies, not conducted by the Applicant and based on another ophthalmic product which has a patent listings, there is the possibility of a patent infringement lawsuit and a delay in the effective approval date of the Azithromycin NDA.

Results of Azithromycin Studies - Cure on Day 6

Azi 63% (n=130)	Vehicle*	50% (n=149)	p=0.03	13.4% (1.9, 25.0%)
Azi 80% (n=159)	Tobra	78% (n=157)	p=0.78	1.5% (-7.4, 10.5%)

*One patient developed a corneal ulcer with subsequent sequelae.

Vehicle Controlled Studies in the Literature

‣Chloramphenicol vs Vehicle (Europe)

•Day 7, Parent evaluation 86% vs 83% -not stat significant

‣Levofloxacin vs Vehicle*

•Day 6, Ophth eval cured 78% vs 61%

‣Norfloxacin vs Vehicle*

•Day 6 Ophth eval improved 88% vs 72%

‣Ciprofloxacin vs Vehicle*

•Day 3 Ophth eval improved 84% vs 65%

‣Polymyxin-bacitracin vs Vehicle*

•Day 3-5 Ophth eval cured 62% vs 28%

•Day 8-10 Ophth eval cured 91% vs 72% -not stat significant

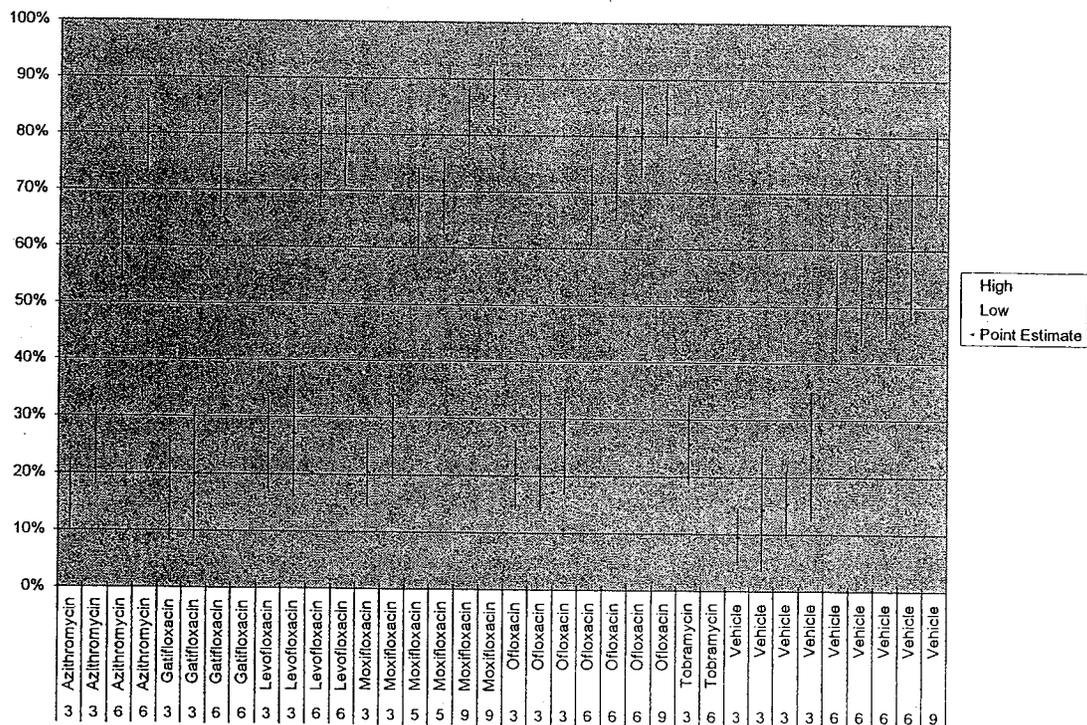
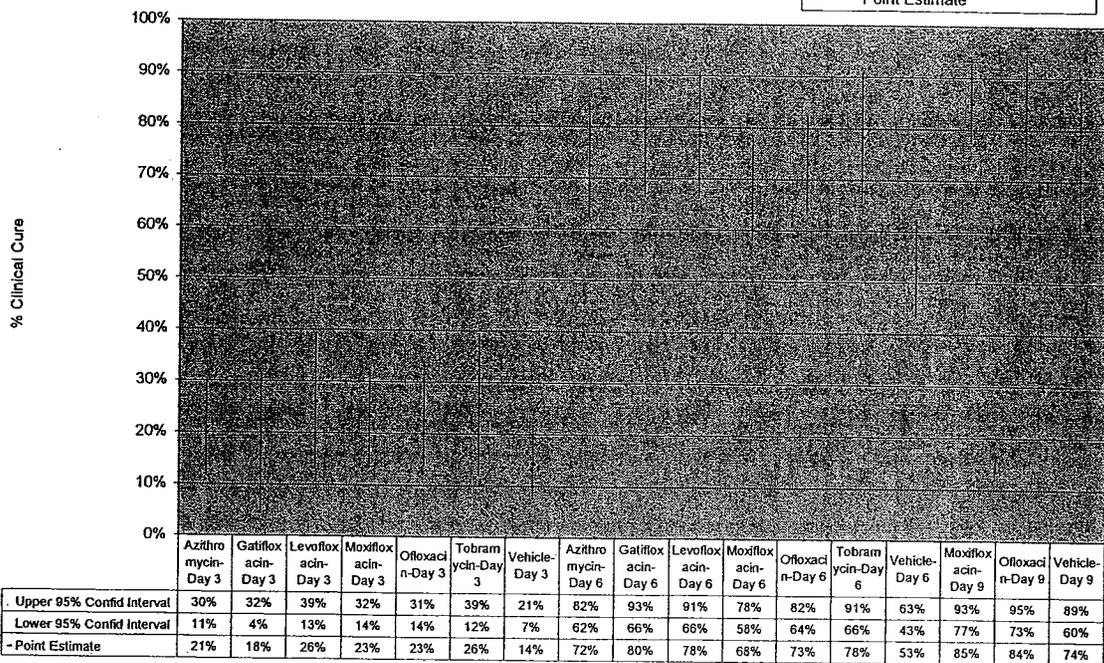
*Study conducted under an IND with results reported to the IND and NDA.

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NDA Studies – Cure Rates

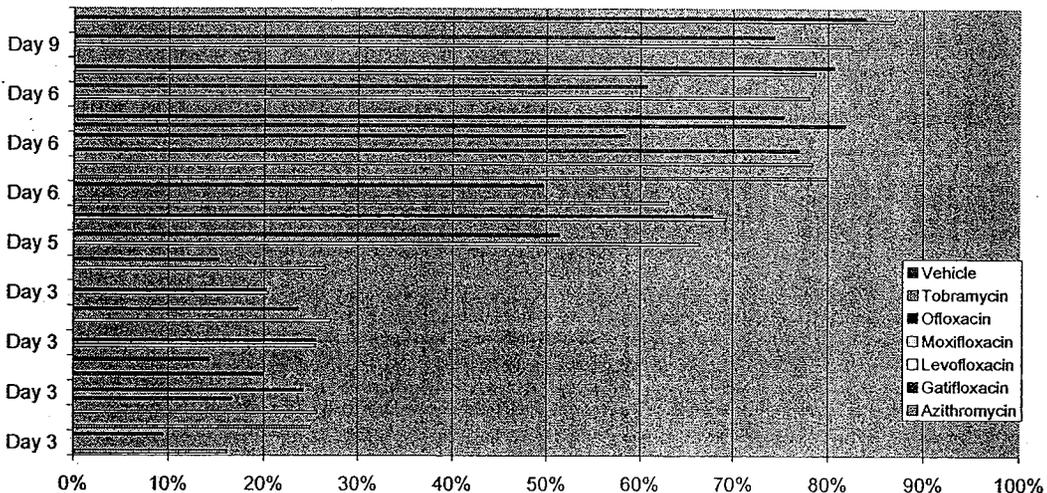
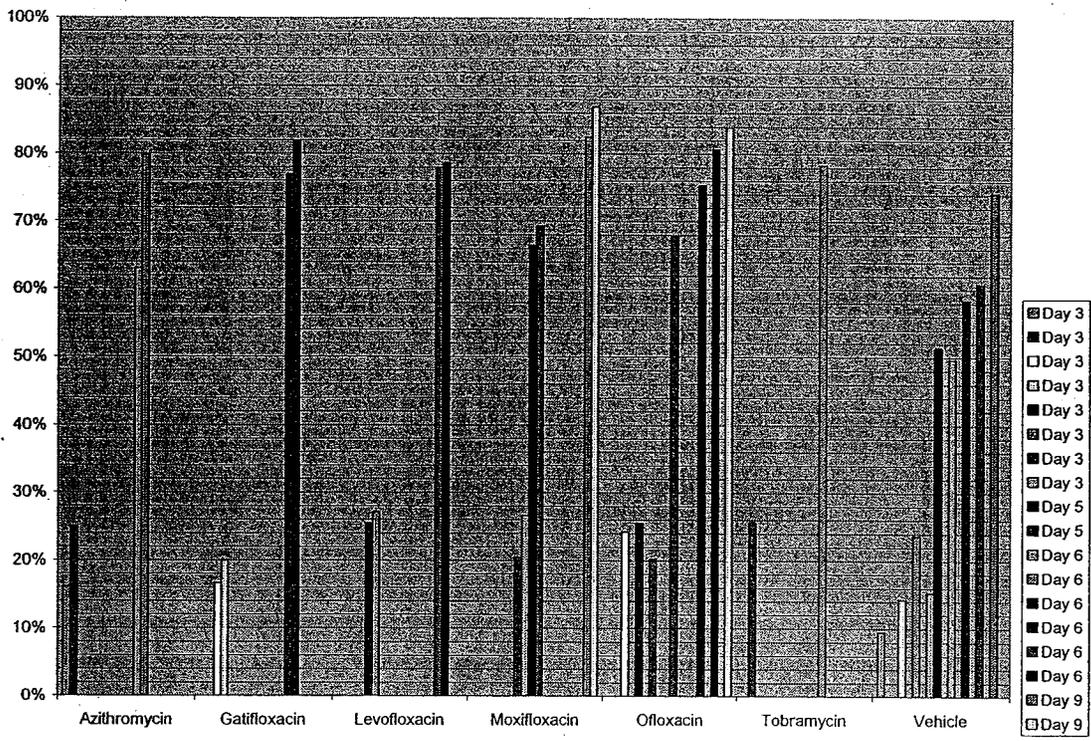
Combined Results from Multiple Conjunctivitis Studies

Upper 95% Confid Interval
 Lower 95% Confid Interval
 - Point Estimate



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NDA Studies – Cure Rates



	Day 3	Day 5	Day 5	Day 6	Day 9	Day 9											
■ Vehicle	9%			14%		24%		15%	51%		50%		58%		61%	74%	
▨ Tobramycin		26%										78%					
■ Ofloxacin			24%		26%		20%			68%			75%		81%	84%	
▨ Moxifloxacin						20%	27%	66%	69%							82%	87%
□ Levofloxacin					25%	27%								78%	79%		
■ Gatifloxacin			17%	20%								77%	82%				
▨ Azithromycin	16%	25%									63%	80%					

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,873

InSite Vision
Attn: William H. Smith, Ph.D.
Sr. Manager, Regulatory Affairs
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Smith:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on April 26, 2006. The purpose of the meeting was to discuss the anticipated NDA filing of ISV-401 AzaSite (azithromycin ophthalmic solution).

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, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

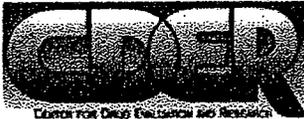
Sincerely,

{See appended electronic signature page}

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

Enclosure

000072



MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2006
START TIME: 12:30 pm
END TIME: 12:55 pm
LOCATION: White Oak, Bldg #22, Room #1419

APPLICATION (DRUG): **IND 62,873**
Drug: ISV-401 AzaSite (azithromycin ophthalmic solution)

INDICATION: Treatment of bacterial conjunctivitis
SPONSOR: InSite Vision, Inc.
TYPE OF MEETING: Pre-NDA meeting

MEETING CHAIR: Wiley A. Chambers, MD
MEETING RECORDER: Raphael R. Rodriguez

FDA Attendees: Wiley Chambers, William Boyd, Lucious Lim, Kimberly Bergman, Martin Nevitt, Fran Weiss, Terry Peters, Yan Wang, Peter Coderre, Michael Puglisi, Alison Rodgers, Raphael Rodriguez

InSite Vision Attendees: Kumar Chandrasekaran, Geoff Langstaff, Erwin Si, Roger Vogel, Mark Abelson, Ping Hsu, William Smith

MEETING OBJECTIVE: To discuss the anticipated NDA filing of ISV-401 AzaSite (azithromycin ophthalmic solution)

SUMMARY OF DISCUSSION:

Responses to the applicant's meeting questions were provided via email April 24, 2006. This meeting served to clarify those responses. The Applicant's questions and the Agency's responses are as follows:

Questions for FDA

1. Does the Agency find the sponsor's proposed indication: "AzaSite is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of (listed) organisms" acceptable?

Response: *The proposed indication is acceptable pending review of the entire clinical trial data set.*

The duration of dosing to the infected eye(s) in the phase 3 clinical trials was 5 days (BID on days 1 and 2, and QD on the following 3 days). The current recommendation for treatment of bacterial conjunctivitis is for a total of 7 days. Trials may be run for less than 7 days, however the label will still reflect 7 days dosing. The proposed package insert (page 15, Dosage and Administration)

b(4)

2. Are the extent and nature of the proposed safety and efficacy data to be submitted adequate to support the proposed indication?

Response: *The proposed safety and efficacy data are acceptable pending review of the entire clinical trial data set.*

On page 68 for efficacy the sponsor has defined clinical resolution as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. Clinical cure should be defined as the complete resolution of conjunctival injection and the complete resolution of conjunctival discharge.

Study C-01-401-003 (page 66) is designed to evaluate the clinical cure of bacterial conjunctivitis and to demonstrate superiority over the vehicle. The sponsor has submitted the recommended per protocol analysis for this trial. Additionally for this superiority trial, the intent to treat analysis must show that the clinical cure rate is not numerically worse than the cure rate of vehicle.

3. Given that the Agency's HL7-SPL Working Group is still trying to develop a schema to incorporate the changes from the Physician's Labeling Rule of January 2006 into the Electronic Labeling Rule (SPL) of November, 2005, will the Division consider allowing the sponsor to submit initial draft and annotated labeling in the old format, and amend the NDA with SPL and draft and annotated labeling in the new format during the NDA review, or propose some other alternative plan?

Response: *The HL7 SPL version 2 schema is an already approved standard that handles labeling in the new PLR format. FDA is working on issuing an implementation guide that will instruct sponsors how to submit SPL in the new format. We are seeking applicants that are willing to work with the SPL implementation team to develop labels in the new format once the implementation guide is available.*

You can submit new PLR format even if the implementation guide is not final by submitting with the original submission draft proposed labeling in MS Word, including both proposed Highlights language and proposed Highlights data elements. If you choose to do this, you should also download and complete prototypical tables for data element organization and include them in your submission. The tables can be found at the following website.

http://www.fda.gov/oc/datacouncil/PROTOTYPE_Stylesheet_with_highlights.pdf

4. Does the Agency find the criteria for requesting a Priority Review compelling?

Response: *This submission is unlikely to receive a priority review. The priority review is intended for products that have the potential for providing some therapeutic advance as compared to already marketed or approved products. Head to head comparisons in clinical studies demonstrating superiority have not been provided.*

5. InSite Vision does not expect that an Advisory Committee will be necessary for this application. Does the Agency concur?

Response: *A decision on an advisory committee meeting will not be made until the application is received and an initial assessment is made. It is considered unlikely that an Advisory Committee will be necessary for this application.*

6. Sponsor intends to submit NDA in an eNDA/CTD Hybrid format whereby the contents will be in CTD format residing in an eNDA defined folder structure with CTD formatted TOCs. The electronic submission will be prepared in accordance with the 1999 FDA guidances, "Providing Regulatory Submissions in Electronic Format – General Considerations," and "Providing Regulatory Submissions in Electronic Format – NDAs" as well as the 2001 Draft Guidance, "Submitting Marketing Applications According to the ICH-CTD Format – General Considerations. Is this Acceptable?

Response: *This is acceptable. However, we are encouraging sponsors to prepare their hybrid submissions following the conventions outlined in the 2005 guidance "Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications" substituting a PDF-based Table of Contents for the XML backbone. Since an increasing number of sponsors are submitting in eCTD format, preparing the hybrid following the eCTD guidance will help facilitate the review process.*

7. Do the proposed format and content of the summaries appear acceptable?

Response: *Proposed format and summaries appear acceptable with the following additional suggestions:*

Please provide the number of patients enrolled (ITT and PP groups) at each site.

Please provide case report forms for all discontinued patients, whether discontinued for treatment or non-treatment related reasons.

8. In Module 5, section 5.3.6 (Reports of Postmarketing Experience) will a simple statement that no topical ophthalmic formulation of azithromycin is marketed anywhere worldwide be satisfactory? Also, because there are no currently ongoing studies, the 120 day safety update report is not expected to contain any new data.

Response: *The statement that no topical ophthalmic formulation of azithromycin is marketed anywhere worldwide will be acceptable.*

If factually correct, you may provide a statement within a 120 day safety update report that there is no new safety information regarding AzaSite since the original submission.

9. InSite is prepared to provide review aids that may facilitate the review process for individual reviewers. Can the Agency identify specifically what review aids would be helpful?

Response: *Documents including study reports and draft labeling provided in WORD format will assist the reviewing process.*

10. In Module 5, sections 5.3.1 (Reports of Biopharmaceutic Studies), 5.3.2 (Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials), and 5.3.3 (Reports of Human Pharmacokinetic Studies) will each contain a request for waiver of studies, citing the Agency's summary review of systemically administered Azithromycin since the subject of this NDA is a non-systemic, topical ophthalmic product. Is this plan acceptable to the agency?

Response: *The Sponsor's plan to submit a request for waiver of studies citing the review of systemically administered azithromycin is acceptable. In the absence of any study, the labeling should assume 100% absorption instead of citing animal studies.*

11. Case Report Tabulations (CRT) will be provided for the two phase 3 trials (placebo-controlled, and active-controlled). For study 001 (phase 1) and 006 (phase 2) modified CRT consisting of a define file, annotated CRF, and raw SAS transport files will be submitted. Is this acceptable to the Agency?

Response: *It is acceptable to have a modified CRT for study 001. Non-modified CRT needs to be provided for phase 2 study 006 and the two phase 3 trails. The statistical analysis plans for the two phase 3 studies also need to be included in the submission.*

12. Do the formatting, presentation, and types of tables and figures in module 2.5 and 2.7 appear to be what is expected?

Response: *The formatting, presentation and tables appear acceptable. Please also refer to the responses in question # 7.*

13. In presenting the incidence of Adverse events in the label, does FDA prefer it be estimated from the reference eye only, or from all treated eyes?

Response: *Adverse events listed within the label are for all treated eyes.*

14. Module 2.7.2.4 summarizes the microbiology information. Will the Agency expect hyperlinks to those studies in the TOC of both modules 4 and 5 since they actually exist in the micro folder?

Response: *Yes, it will make it much easier and navigable for the reviewers to review and evaluate the e-CTD.*

15. In the ISE the sponsor plans to present the efficacy results for the combined PP data set from studies C-01-401-003 (vehicle-controlled phase 3) and [C-01-401-004 (active-controlled phase 3) only, and provide links to the efficacy results for the other data sets (EE, ITT and ITT2) in the respective Clinical Study Reports. Is this approach acceptable?

Response: *Studies 003 and 004 should not be combined for efficacy. It is more appropriate for the ISE to provide hyperlinks to the full study reports. Each study report should include analyses based on observed data alone (without imputation for missing data) and the efficacy results based on treating missing data as failure in addition to an intent-to-treat analyses with the last observation carried forward.*

16. In the ISS the sponsor plans to present the combined safety results for the Safety Data Set only from the phase 3 studies (003 and 004 as above), using a Safety Data Set comprised of all patients who received at least one dose of study drug. A separate safety analysis combining data from phase 1 (study 001) and phase 2 (study 006) trials which used a different formulation and regimen will be provided in support of the ISS. Is this acceptable to the Agency?

Response: *Yes.*

Addendum:

1. *The sponsor would like to submit draft labeling in MS Word with the 2 column format. Acceptable.*
2. *The division prefers electronic files in the 5-module format. The microbiology section references will be in module 5 with hyperlinks in module 4.*
3. *The sponsor is required to present all reported adverse events for all patients, all eyes.*

4. *The division needs the raw and derived data for the purpose of performing confirmatory analysis. The sponsor agreed to provide full CRTs for study 006 (phase 2).*

APPEARS THIS WAY ON ORIGINAL

**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
5/10/2006 04:50:23 PM

000079



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,873

InSite Vision
Attention: Geoff Lanstaff, Director of Quality
965 Atlantic Avenue
Alameda, CA 94501

Dear Mr. Langstaff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AzaSite (azithromycin ophthalmic solution), 1%.

We also refer to the meeting between representatives of your firm and the FDA on June 21, 2005. The purpose of the meeting was to discuss the upcoming NDA submission for the product.

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, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology
Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

000066

MEETING MINUTES

Division of Anti-Infective and Ophthalmology Products, HFD-520

Meeting Date: June 21, 2005

Time: 10:30 AM EST

Application: IND 62,873

Meeting Type: Pre-NDA

Drug: AzaSite (azithromycin ophthalmic solution, 1%)

Sponsor: InSite Vision

FDA PARTICIPANTS:

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b(6)

BACKGROUND INFORMATION: The Division provided InSite draft responses to these questions via fax on June 17, 2005. This meeting was held to clarify only a few issues.

Topics for discussion in this pre-NDA meeting include CMC, non-clinical and overall formatting adequacy for the proposed NDA application for the treatment of bacterial conjunctivitis. The application is planned for submission in March 2006.

QUESTIONS

1. Are the proposed release and stability specifications for the Product acceptable?

Response: No. Identification should be reported with either a specific test or at least two nonspecific tests. Impurities should be reported as specified, any individual unspecified and total. The particulate matter test should be conducted during stability at least once a year.

2. Are the presentations for the stability protocol and tabular data summaries acceptable to complete critical review of the data?

Response: No. The stability protocol needs the inclusion of a stability commitment paragraph for the reporting and discussion of any lot(s) that fall outside the approved acceptance criteria.

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See "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" February 1987, Page 4.

The column "3 mos @ 25 °C" in the stability tables needs clarification.

3. The validation master plan of the commercial process is included. Is this plan acceptable?

Response: This is a cGMP issue. We recommend you contact the local FDA District Office.

4. We will present 12 months real time stability data on CTD submission and update stability during the review process. What dating can we expect from data to be presented?

Response: This is a review issue that will be addressed during the review cycle. Assuming that the product demonstrates stability, 12-18 months dating would be expected from 12 months of real time stability data.

5. Does FDA agree on the format and content of Module 2.4?

Response: It appears OK in general, but the Microbiology information belongs in the clinical Module under Clinical Pharmacology Studies, Special Studies (Module 2.7.2.4).

6. In Section 2.6.2, we plan to cross-reference to NDA 50-670 with regard to classical primary and secondary pharmacodynamics, as well as safety pharmacology. Does FDA agree?

Response: It is not clear from your submission if you will have a letter of authorization from Pfizer allowing the Agency to reference their data on your behalf. You may "cross reference" data from any NDA if you have a letter authorizing you the right to reference data in their NDA. The use of data in this fashion is consistent with a 505(b)(1) application, as opposed to a 505(b)(2) application. The Agency can not rely on data that belongs to another sponsor without their permission. Unless you submit a letter from Pfizer authorizing you to cross reference their NDA(s), please do not use the term "cross reference" in your NDA submission.

If you do not have a letter of cross reference, you may refer to the Agency's summary findings from an NDA, if you submit a 505(b)(2) application and follow the appropriate notifications listed in section 505(b)(2) of the Food Drug and Cosmetic Act and its implementing regulations. As noted above, this is not considered "cross-reference."

In either case, if you do not conduct any additional non-clinical studies, you should comment in your application on why you believe that the data is sufficient and that additional studies on your specific product are unnecessary.

7. In Section 2.6.4, we have revised the data as described in the TOC in the table below that differs from the standard CTD. InSite proposes that this revised organization to the TOC would allow a better flow of data. Does FDA agree?

PROPOSED CTD TOC	STANDARD CTD TOC
2.6.4 Pharmacokinetics Written Summary	2.6.4 Pharmacokinetics Written Summary
2.6.4.1 Brief Summary	2.6.4.1 Brief Summary
2.6.4.1.1 Systemic Pharmacokinetics	2.6.4.2 Methods of Analysis
2.6.4.8 Other Pharmacokinetic Studies	2.6.4.3 Absorption
	2.6.4.4 Distribution
	2.6.4.5 Metabolism
	2.6.4.6 Excretion
	2.6.4.7 Pharmacokinetic Drug Interaction
	2.6.4.8 Other Pharmacokinetic Studies

Response: The proposed revision is acceptable; however, as noted above, the microbiology data (such as that in your draft table 2.6.1.1) does not belong in this section.

8. Ocular pharmacokinetic studies were strategically placed in Section 2.6.4.8: "Other Pharmacokinetic Studies" because we believe that Sections 2.6.4.1 to 2.6.4.7 are reserved for systemic pharmacokinetics. Does FDA agree?

Response: The plan is acceptable, although sections 2.6.4.1 through 2.6.4.7 are not reserved for systemic pharmacokinetics.

9. InSite intends to file tabular summaries, like the one in Table 2.6.7.1 to the nonclinical section of the NDA. Column headers and appropriate inserts will be incorporated. Does FDA agree?

Response: Acceptable.

10. It is InSite's understanding that Module 4 is a repository of study reports and literature from the nonclinical area. As such, we do not plan to add any summary text to the section. We will insert the study reports in the appropriate sections. With regard to the paper from the literature, we plan to insert them in alphabetical order in Section 4.3: LITERATURE REFERENCES. Does FDA agree?

Response: Acceptable.

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Additional Comments

You may contact the Central Document Room (301-210-2884) at any time to receive your NDA number assignment. It will be helpful to have your NDA number on your application when it is submitted. When contacting them please say that your application is an old antibiotic and you should receive a 50,000 assignment.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Janice Soreth
7/15/05 11:31:53 AM

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DRAFT MEETING MINUTES TO SPONSOR
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

These comments are being given to as a courtesy prior to our formal meeting on April 27. If you understand our responses and feel they warrant no further discussion, the meeting could be cancelled. If you do wish to still have the meeting, please remember we will not entertain any new questions or documentation for that meeting. If you wish to discuss any new information another meeting request should be submitted.

MEETING DATE: April 27, 2005

TIME: 11:00 EST

Application: IND 62,873

DRUG: ISV-401 Azithromycin

SPONSOR/APPLICANT: InSite Vision

MEETING TYPE: EOP2

BACKGROUND INFORMATION: Phase 3 clinical trials for this application were started last summer. The sponsor has a number of questions regarding finalizing the Statistical Analysis Plan and clinical microbiological requirements. There are also questions about submitting in CTD format.

QUESTIONS

Clinical Questions

1. All treatment emergent adverse events will be reported in individual study listings (as discussed in ICH Guideline E3, Structure and Content of Clinical Study Reports, Report Section 16.2). For each Phase 3 study, C-01-401-003 (A Study to Evaluate the Clinical and Microbial Efficacy and Safety of 1.0% AzaSite™ Compared to Vehicle in the Treatment of Bacterial Conjunctivitis) and C-01-401-004 (A Study to Evaluate the Clinical and Microbial Efficacy and Safety of 1.0% AzaSite™ Compared to 0.3% Tobramycin Ophthalmic Solution in the Treatment of Bacterial Conjunctivitis), we will also tabulate the frequency and severity of adverse events by McDDRA SOC, HLT, and preferred term. Probability testing of between group comparisons will be performed only on cells with an incidence $\geq 5\%$ of the total population. Is this acceptable?

Response: Acceptable.

2. We plan to stratify efficacy in our Phase 3 studies by age. We would stratify the age into four groups: 1-11, 12-16, 16-64 and ≥ 65 . Is this acceptable?

Response: Acceptable. There are no known differences in the disease between children and adults, data can generally be extrapolated from pediatric patients to adults and vice versa. The Division also expects to see overall efficacy tables without stratification and a listing of the number of children under 12 by year of age.

3. We plan to stratify efficacy in our Phase 3 studies by iris color. We would stratify the iris color into two groups: dark and light. Dark iris color includes only the brown iris and light iris color includes all other iris colors. Is this acceptable?

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Response: No. There are some hazel eyes which would also be dark.

4. Consistent with FDA guidance "Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions", all datasets will be presented in SAS format and the data will be provided as SAS (Version 6 or later) transport files. Is this acceptable?

Response: Acceptable.

5. We plan to submit the New Drug Application (NDA) in a paper Common Technical Document (CTD) format. Following that format, would the FDA prefer to see the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) in Module 5 and summarized in Module 2.7, or fully incorporated into Module 2.7?

Response: The Division prefers the ISS & ISE be submitted in Module 2.7 unless you have a reason to submit it specifically in Module 5.

6. For the clinical studies section of the package insert, we plan to present clinical cure rates and microbial eradication rates from our Phase 3 studies C-01-401-003 and C-01-401-004. We do not plan to integrate the Phase 2 study because it was conducted with a different formulation. Is this acceptable?

Response: Comments on labeling will need to be deferred until the studies have been reviewed.

7. For the adverse reactions section of the package insert, we plan to present integrated data over the two Phase 3 studies (C-01-401-003 and C-01-401-004). We will also present the safety experience with our pilot formulation in Phase 1 (normals) and Phase 2 (symptomatic patients) (COSTART), but we do not plan to integrate these data with our Phase 3 studies because these studies were conducted with a different formulation. Is this acceptable?

Response: Comments on labeling will need to be deferred until the studies have been reviewed.

Additional Comments:

Regarding Protocol C-01-401-004, the Division strongly suggested the addition of a third arm to the trial comprised of subjects dosed with AzaSite QID on Days 1-5.

The case report forms for all discontinued subjects in controlled clinical studies pertinent to the claimed indication, regardless of cause, should be included in the NDA submission.

If the sponsor wishes to provide documents in WORD format (for the relative ease of transfer of text, tables, and images) these electronic files can be given to the project manager as a desk copy. Labeling of the drug product will be for at least 7 days.

Optometrists are not considered experts and are not necessarily qualified to perform the necessary ophthalmic examinations.

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Clinical Microbiology

1. Azithromycin has been studied extensively, resulting in a large body of literature. To review and present an analysis of all the available literature would produce a massive document. We suggest that summaries and reviews of only the key literature (e.g., those listed in the References section of this document and those pertinent to ocular use) be used to present the salient points for each of the microbiology areas to be covered as outlined in Table 1. Is this sufficient for the FDA?

Response: Without viewing the intended data, it is not possible to determine if the data is sufficient for submission of the NDA. The Agency recommends that you provide the pertinent data and publications that are intended to support the NDA. We remind you that MIC data for the spectrum of activity section of the Microbiology section should include data from more than one study and should include at least 100 recent (within the last three years) clinical isolates. These data should include MIC_{50s}, MIC_{90s}, and MIC ranges. These data may be generated by you or cited from the literature.

2. The rationale for the proposed broad in vitro spectrum study is that limited current data exist for many of these organisms, as they are not routinely tested in clinical laboratories; they are considered out of spectrum for typical azithromycin "systemic" use. We recognize that organisms to be included in the in vitro list should be organisms that would potentially be a) pathogens found in indications that the drug will be approved for and b) pathogens for which the MIC₉₀ should be at or below the susceptible breakpoint.
 - a) This group of organisms has been listed in the Vigamox and Zymar label, and therefore, are presumed ocular pathogens. Is this presumption acceptable to the FDA?
 - b) It may not be possible to assemble 100 isolates for each species. Is the number of isolates listed in the study (Section 2.1 of this document) sufficient?

Response: Organisms listed in each list should be ocular pathogens. It is correct to presume that FDA believed the organisms listed on the labeling were ocular pathogens at the time of the approval.

As mentioned previously, MICs from 100 recent clinical isolates are necessary for inclusion on the in vitro list of the Package Insert. These MICs may be generated by you or may be cited from literature.

3. The ocular formulation of azithromycin, AzaSite, leads to very high levels of drug in the target tissue (C_{max} of 83 ug/mL), which is significantly higher than the current breakpoint levels. "Systemic use" breakpoints may well underestimate the spectrum of activity of AzaSite. We will, in our analyses of MICs and bacteriologic outcome, want to explore the possibility of potential new interpretive test criteria to apply to organisms which previously were considered outside the spectrum of "systemic" azithromycin. Will the FDA consider organisms that have MIC_{90s} greater than the susceptible "systemic" breakpoint of ≤ 2 ug/ml, but lower than the C_{max} following ocular administration, to be included in the in vitro list?

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Response: Prior to submission of the NDA, is advisable to submit a plan for analyses of MICs and bacteriologic outcome as well as the plan for potential new interpretive test criteria to apply to organisms which previously were considered outside the spectrum of "systemic" azithromycin. Breakpoints are not utilized in the same manner for topical anti-infectives as systemic.

Second, the inclusion of organisms on the second list is based upon MIC₉₀ values less than or equal to the clinically relevant susceptible breakpoint established for the particular genera or species. Thus, only those organisms with MICs less than the established breakpoints for azithromycin will be considered for the second list

4. We will not attempt to establish new susceptibility test systems. Our goal is to use currently recognized and approved ones. The clinical study susceptibility data will consist of MIC data only generated by standard NCCLS (CLSI) reference test methods or by FDA approved commercial test systems. Is this sufficient for the FDA?

Response: Yes, data generated by standard CLSI reference test methods or FDA approved commercial test systems are acceptable.

5. Is the design of the "In Vitro Studies Conducted During the Clinical Trials" (presented in Section 9 of this document) acceptable to the FDA?

Response: Data from these studies should include MICs for the comparator, tobramycin, in clinical trial C-01-401-004. MICs for each study should be presented in tabular form "per pathogen" with data for both clinical cure and bacterial eradication.

6. Is "Overall Plan for Microbiology Studies for AzaSite" (Section 1 of this document) sufficient to support an NDA/CTD submission of AzaSite? If the plan is not sufficient, what additional studies are needed?

Response: As a general plan, the "Overall Plan for Microbiology Studies for AzaSite" contains an adequate outline for studies completed and to be completed that should generate data for the submission of a NDA. However, this does not represent an endorsement of the data that will be presented to result in an approval of the NDA. The adequacy of the data can only be determined after review. This Reviewer recommends the following. First, please present data from the NDA cited as summary tables in the NDA submission.

Second, please provide a summary of the epidemiological studies derived from susceptibility patterns of the pertinent organisms to azithromycin. In a recent report, Mino de Kaspar et al. (2005) found evidence that resistance to azithromycin was higher among preoperative normal conjunctival bacteria than for other antibiotics. Greater than 40% of coagulase-negative Staphylococci (124 isolates) and greater than 80% of multiresistant bacteria (43 isolates) were resistant to azithromycin. In both cases, the only other greater antibiotic resistance was to penicillin. In addition, azithromycin resistance was high among ocular pathogens such as group 1)

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Streptococci (100% of 8 isolates) and Gram-negative rods (36% of 11 isolates). Thus, the potential for the development of resistance to azithromycin is real and should be monitored.

7. Our current plan is to submit the paper NDA in CTD format. We plan to place Sections 2 to 7 of this document (from "Antimicrobial Spectrum of Activity" to "Animal Therapeutic and Pharmacologic Studies") in Section 2.6.2 of the CTD, Section 8 of this document ("Ocular Bioavailability Studies") in Section 2.6.4 of the CTD, Section 9 of this document ("In Vitro Studies Conducted During the Clinical Trials") in Section 2.7.3. of the CTD, and the actual studies and publications that are summarized there in Module 4. Is this arrangement acceptable?

Response: To facilitate the review of the NDA, it is advisable to include all pertinent Microbiology data together in the same section of the NDA in the CTD format. The Reviewer prefers that all pertinent Microbiology data, including all preclinical and clinical data be supplied in the section 2.7 of the Clinical Summary, specifically, section 2.7.2.4, Special Studies of the CTD format. For more details, please see the Agency guidance document "Guidance for Industry-M4E: The CTD-Efficacy".

APPEARS THIS WAY ON ORIGINAL

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MEETING MINUTES

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

MEETING DATE: January 15, 2003 **TIME:** 10:30 AM EST

Application: IND 62,873

DRUG: ISV-401 Azithromycin

Meeting Request Submission Date: October 10, 2002

Meeting scheduled: October 16, 2002

SPONSOR/APPLICANT: InSite Vision

Date Sponsor Requested: January 2003

MEETING TYPE: EOP2

Briefing Document Submission Date: December 16, 2002

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Kumar Chandrasekaran, CEO

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MEETING OBJECTIVES:

BACKGROUND INFORMATION: Insite has completed a Phase 1 safety study and a pilot Phase 2 efficacy study. Also a 1 month toxicity study in animals was completed and submitted to the IND in September 2002. Insite plans on initiation of Phase 3 studies early in 2003.

QUESTIONS

CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

1. The manufacture and process validation plan for ISV-401 is described, in sequence, as follows:
 - Phase 3 supplies will be manufactured using a [Redacted], followed by the manufacture of three registration batches, using the same [Redacted]. Summaries of scale-up, process, and stability data of the registration batches will be submitted to the NDA.
 - Perform process scale-up from [Redacted] batch size intended for commercial scale.
 - Process validation will be performed on the [Redacted] commercial batch rather than on the [Redacted] batch.
 - Manufacture of three [Redacted] batches.
 - Process validation report and 3-month accelerated stability data from the three commercial batches will be available at the pre-approval inspection.

b(4)

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- a) Is the manufacturing plan acceptable for the NDA submission and pre-approval inspection?

Response: Yes, this manufacturing plan is acceptable for submission and pre-approval inspection. Please note that the 3-month accelerated stability data from the three commercial batches should be submitted in the NDA while the process validation report should be kept on site for pre-approval inspection.

- b) Is the 3-month accelerated stability data from the [redacted] batches and the available stability data (12 months data) from the three [redacted] registration batches enough to bridge the stability programs between the [redacted] and the [redacted] batch process?

b(4)

Response: Yes. The proposed data is sufficient for the scale-up program.

- c) We should have at least 2 years stability data on the 12-liter batches (clinical supplies for Phase 1 and Phase 2 studies) by the time for NDA submission. If the products were stable, would 6 months real time stability data be sufficient at the time of NDA submission for the registration batches?

Response: Please clarify if the market product is used in the stability batches. If not, delineate the differences. Six months of real time stability data from the registration batches may be acceptable, if justified, according to ICH Q1C. In addition to supporting stability data from clinical batches, the justification may include known stability profile of an approved product containing the same chemical entity in a similar dosage form. However, expiration dating period will be based on the submitted data.

- d) Primary container has a volume of [redacted], and it is designed for a maximum fill volume of [redacted]. The proposed fill volume for ISV-401 is [redacted] 2.5 ml. Are both volumes acceptable for this container? If we conduct stability studies with [redacted] fill volume, would the studies support fill volumes of [redacted] and 2.5 ml for commercial product?

b(4)

Response: Yes, The [redacted] fill stability studies are acceptable in support of the [redacted] and 2.5 mL fill for commercial product. Weight loss data should be included in the proposed stability studies.

- e) We plan to use a tan colored cap as part of the primary packaging for ISV-401. Is this acceptable?

Response: Yes this is acceptable

- f) Is DMF No. [redacted] adequate for supporting drug substance information for NDA submission?

b(4)

Response: This is a review issue and as such, will be dealt with during the NDA's review cycle.

- g) Formulation development history was briefly described under "Formulation Linkage" in this package. During the development process, different formulations with minor adjustments were used in preclinical and clinical studies. These minor differences in formulations should not affect the outcome of the previously conducted studies, and these studies can support

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future Phase 3 studies without additional bridging studies. Do you agree with the above statements?

Response: Yes this is agreeable to the agency.

- h) Particulates test method and specifications were developed based on your input from the Pre-IND Meeting. Is it acceptable?

Response: Yes this is acceptable.

PRECLINICAL

1. A one-month ocular toxicology study was conducted with ISV-401 containing drug source from [REDACTED]. A 14-day ocular toxicology study was conducted with ISV-401 containing drug source from [REDACTED]. Phase 3 supplies will be manufactured with drug source from [REDACTED]. Are the ocular toxicology studies adequate to support the Phase 3 trials and NDA submission? b(4)

Response: Yes, provided that:

- a. *The impurity profiles are similar.*
 - b. *Formulation is the same as the clinical formulation. Or, ocular effects of inactive ingredients are known.*
2. No additional preclinical studies (including toxicology studies) are planned in the future. Is overall preclinical program adequate for a 505(b)(2) NDA submission?

Response: Yes (see answer to previous question)

MICROBIOLOGY

1. The Pre-IND Meeting Minutes state that it is acceptable to reference the literature and the Zithromax NDA 50-670 to support the *in vitro* microbiology section of the label for bacteria not cultured in clinical studies. Can ISV-401 claim the *in vitro* activity against these microorganisms listed in the Microbiology Section?

Response: Organisms that are not necessarily bacterial conjunctivitis will not be listed in the label. MIC₉₀ data should not be more than 5 years old to reflect antibiotic resistance changing patterns. An algorithm followed by the Anti-Infective division for labeling guidance is attached the end of this document.

CLINICAL

1. In our pilot Phase 2 study, ISV-401 demonstrated a bacterial eradication rate of 90% and a clinical resolution rate of 70% after dosing BID on Day 1 followed by QD on Days 2, 3, 4, 5. Due to our small sample size, no significant difference was seen between ISV-401 and vehicle. Is there a minimal bacterial eradication rate and clinical resolution rate required for approval? If these rates are achieved is it a requirement to show a significant difference from vehicle?

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Response: Ophthalmic drugs developed for the treatment of bacterial conjunctivitis will be evaluated as follows:

If the sponsor uses the vehicle as control, the agency expects to see two replicative trials showing superiority to vehicle in clinical cure rate in the per protocol analysis. Clinical cure is defined as the resolution of signs and symptoms (i.e. a score of 0).

An alternative approach is to show superiority to vehicle in one trial and equivalence to tobramycin or one of the approved fluoroquinolones in another trial. Equivalence should be demonstrated by showing that the 95% confidence interval for the difference in success rates is within $\pm(1-p_c)$ where p_c is the clinical cure rate. If p_c is less than 80%, the CI must be within ± 0.2 .

Additionally, the intent to treat analysis must show that the clinical cure rate is not inferior to vehicle.

In-vivo eradication rates will be used to determine the contents of the indication section of the labeling. Criteria for inclusion usually are:

- *Organisms that are cultured from an eye with conjunctivitis and treated with the drug in a clinical trial in 5 or more cases with a $\geq 80\%$ eradication rate*
 - *Organisms that are cultured in less than 5 infections are not listed in the label.*
2. Due to our unique formulation of ISV-401 (azithromycin in DuraSite), our preclinical studies, and our Phase 2 study, InSite Vision believes ISV-401 is effective with a dosing regimen of [REDACTED]. This unique dosing regimen is similar to the systemic administration of oral azithromycin (Zithromax). We were told in our pre-IND meeting that we would not be able to obtain a labeling claim with this dosing regimen. Can we obtain a labeling claim with a dosing regimen of [REDACTED]?

b(4)

Response: The current recommendation for the treatment of bacterial conjunctivitis is for a total of 7 days. Trials may be run for less than 7 days, however the label will still reflect 7 days of dosing. Based on the clinical response in the previous study, consideration should be given to increasing the dosing frequency.

3. Can the Phase 3 active control study be considered a non-inferiority trial rather than an equivalence trial?

Response: No. It should be an equivalence trial. See Clinical question #1.

4. InSite Vision plans to use 0.3% tobramycin solution as the active control in one of the Phase 3 trials. Is this acceptable? Can generic tobramycin be used, or are we required to use Tobrex solution?

Response: Tobrex solution is acceptable. A generic product may be acceptable. The specific source should be submitted with the full protocol in the IND.

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5. The labeling for tobramycin states the dosing as 1-2 drops every 4 hours and in severe infections, 2 drops should be instilled every hour. Based on this labeling, is it acceptable to dose 1 drop of tobramycin QID for five days in our Phase 3 study?

Response: Acceptable.

6. Since the dosing regimen for ISV-401 is different from tobramycin, InSite plans to mask the study as follows:

<u>Day 1</u>	<u>ISV-401 group</u>	<u>Tobramycin group</u>
Dose 1	ISV-401	tobramycin
Dose 2	Vehicle	tobramycin
Dose 3	Vehicle	tobramycin
Dose 4	ISV-401	tobramycin

<u>Days 2 through 5</u>	<u>ISV-401 group</u>	<u>Tobramycin group</u>
Dose 1	ISV-401	tobramycin
Dose 2	Vehicle	tobramycin
Dose 3	Vehicle	tobramycin
Dose 4	Vehicle	tobramycin

Is this masking plan acceptable?

Response: Acceptable

7. InSite Vision may plan to conduct the active controlled study in Europe. We have been told that it may be possible that the European regulatory agencies may require different time points for evaluation of efficacy for product approval in Europe (e.g., Evaluation at Day 6+1 day and Day 8+2 days, as opposed to Day 3+2 days and Day 7+2 days). Is it acceptable for product approval if the active controlled study has different time points for evaluation than the vehicle controlled study?

Response: The trials should have the same time points for evaluation of the primary efficacy endpoints. Day 3 should be ± 1 .

8. Can we submit adverse event tables in NDA using the COSTART dictionary?

Response: Acceptable, as long a table linking the COSTART terms with the verbatim responses is included.

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9. During our pre-IND meeting, we were told that visual acuity should be obtained by age appropriate methods. We had defined this as follows:

- No VA measurement required for children under 3 years of age
- Lea Symbols[®] for individuals 3 years of age and older who cannot reliably use the Snellen chart

Is this definition acceptable?

Response: No. We expect for investigators to make an effort to get a visual acuity measurement in all patients. We do not agree with not making VA measurement a requirement for patients under the age of 3. Lea Symbols are acceptable for those patients that cannot reliably use a Snellen chart

10. What is the definition of a clinically significant change in VA? Is it ≥ 2 Snellen lines or ≥ 3 Snellen lines?

Response: We consider a clinically significant change to be a doubling of the visual angle (equivalent to at least 3 lines on an ETDRS chart).

11. InSite Vision plans to conduct the vehicle-controlled Phase 3 Study #C-01-401-003 in the United States and the active-controlled Phase 3 Study #C-01-401-004 outside the United States (most likely in Europe and Canada). Is this acceptable?

Response: Acceptable. It is important that the demographics of the study participants be reflective of the US population and that at least one of the clinical studies be conducted in the US to ensure that bacterial organisms found in the US are adequately treated.

12. Is our study design for the pharmacokinetic study C-01-401-005 acceptable?

Response: The protocol is inadequate because the subject population is healthy volunteers. Local inflammation associated with bacterial conjunctivitis could cause an increase in local bioavailability due to the vasodilatation of the ocular blood vessels which would not be addressed in this study.

The possibility of obtaining a waiver of in vivo biostudies exists based on the PK results of IV administration of azithromycin. We would be willing to discuss this approach with you in the future.

13. Are the completed studies together with successful completion of the proposed studies sufficient to achieve approval of ISV-401 for the indication of bacterial conjunctivitis?

Response: Determinations of approval can only be made after submission and review of an NDA.

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14. Does FDA have any additional comments on the clinical program?

Response:

- *For labeling down the age of 1 year, the trials should be conducted in at least 5 one-year old patients.*
- *The division will evaluate the efficacy of this product based on the clinical cure rate. The eradication rate as proposed will be evaluated separately.*

Additional Comments

Include name, address, name of contact person and establishment facility number for all manufacturing facilities in the NDA. Include telephone and fax numbers for the contact person.

All manufacturing facilities should be ready for inspection at the time of NDA submission.

The Division noted no other specific comments.

See attached signature page

Lori Gorski
Project Manager

Wiley Chambers, M.D.
Deputy Director

MEETING MINUTES

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Anti-Infective Algorithm - Attachement

The microbiology subsection of the label contains two lists of organisms:

The first list is based on pathogens evaluated during clinical studies and approved for inclusion in the INDICATIONS AND USAGE section.

The second list is based on in vitro susceptibility test data whose clinical significance has not been determined in adequate and well controlled clinical trials.

The in vitro information submitted in support of the second list should be presented as a summary for each species proposed for inclusion. The summary should include:

- 1) The relevance of the pathogen to the approved indication(s).
- 2) The frequency in which the pathogen is shown to cause disease in the general population.
- 3) Relevant literature reference summary tabulations (range, MIC₅₀, MIC₉₀) of the susceptibility data of the pathogen and annotated supporting literature.
- 4) A summary of the methods and their comparability used to assess susceptibility as described in the supporting literature.
- 5) Comparisons of US and foreign data analyzed separately and together.

Organisms to be included in the second list must have MIC₉₀ less than or equal to the clinically relevant susceptible breakpoint.

The criteria to be considered in the development of this second list are as follows:

1. Scientific evidence should be provided which demonstrates that an organism is a frequent pathogen for an approved indication. Appropriate references, such as the FDA/Infectious Disease Society of America (IDSA) Guidelines⁹, the FDA Evaluability Guidelines and published literature should be used. Inclusion of a pathogen must be supported by a reasonable number of associated and adequately described clinical cases published in the scientific literature.
2. The species to be included in the second list must be supported with susceptibility testing of recent clinical isolates. The definition of recent depends on whether the antimicrobial is a new molecular entity (NME) as described by the FDA or an approved antimicrobial.

a. If the antimicrobial is a NME, the strains used to generate the data should span no more than 5 years from the date of submission of the NDA. For the common species, at least 100 strains derived from broad geographic regions of the United States should be provided. For the fastidious or less frequent isolates, a case by case assessment of the number required will be performed. These data will be used to monitor changes in the susceptibility profile. If foreign in vitro susceptibility data are to be presented, the data from U.S. and foreign sites should be presented separately. Only 25% of the isolates used to make the assessment of inclusion in list #2 can come from foreign studies. It is preferable that NCCLS susceptibility test methods be used for isolates from foreign studies. Acceptance of foreign data may be based on comparability of methods used to generate the susceptibility data and similarity of the susceptibility test results for isolates evaluated.

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b. If it is an approved antimicrobial, then the sponsor should provide relevant and comprehensive surveillance data and published literature. The age of the strains used to generate the data should not be older than 4 years prior to submission of the application. However, considering resistance development data, more recent results would be of greater importance. For surveillance data, the sponsor should provide the name of the organization conducting the studies, their capabilities, pertinent standard operating procedures, and the geographic origin(s) of the data. We would encourage the establishment of a Drug Master File (DMF) for these surveillance facilities. Literature from refereed journals should provide the origin(s) of the data (geographic region, reference lab), test methods used, and methodology quality control to assure confidence in the data. Publications submitted should provide an overview of MIC ranges, MIC₅₀, MIC₉₀ and histograms.

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this page is the manifestation of the electronic signature.**

/s/

Wiley Chambers
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MEETING MINUTES

Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products

MEETING DATE: April 9, 2001

TIME: 1:30 PM

DRUG: azithromycin (ISV-401) in the DuraSite delivery system
SPONSOR/APPLICANT: Insite Vision
TYPE of MEETING: Pre-IND/EOP2

Meeting Request Submission Date: January 11, 2001
Date Sponsor Requested: March 29, 2001
Briefing Document Submission Date: March 16, 2001

FDA PARTICIPANTS:

Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
Linda Ng, Chemistry Team Leader
Li Rodriguez, Chemistry Reviewer
Su Tso, Chemistry Reviewer
Stan Lin, Statistical Team Leader
Jennifer Harris, Medical Officer
Lucious Lim, Medical Officer
William Boyd, Medical Officer
Mike Puglisi, Project Manager
Raphael Rodriguez, Project Manager
Joanne Holmes, Clinical Reviewer
Harold Silver, Clinical Microbiology

INDUSTRY PARTICIPANTS:

Raymond Chen, Sr. Director Regulatory Affairs
Erwin Si, Sr. Director Pre-Clinical Development
Samir Roy, Sr. Director Pharm. Development
Cheryl Eto Chen, Sr. Director, Clinical
Consultant
VP Clinical

b(6)

MEETING OBJECTIVES: To provide development guidance for azithromycin as ocular antibiotic used in the Dura-site delivery system for allergic conjunctivitis.

BACKGROUND INFORMATION: Currently, azithromycin is approved as NDA 50-670, Pfizer's Zithromax capsules. Insite Vision is pursuing development for an ocular administration.

QUESTIONS

Chemistry, Manufacturing and Control Information

1. Is the information in DMF No. (Azithromycin USP) adequate to conduct phase I/II clinical trials? Is there any additional information needed from under this Drug Master File in order to qualify this Azithromycin as a drug source?

b(4)

Response: We do not know the answer until we are authorized to review and have had a chance to review the DMF. However, the impurities testing is encouraged to meet ICH Q3A criteria, the values set for acceptance criteria should be based on actual data.

2. The storage conditions on Xalatan's label reads:

"Protect from light. Store unopened bottle under refrigeration at 2°C to 8°C (36° to 46°F). Once opened the 2.5 ml container may be stored at room temperature up to 25°C (77°F) for 6 weeks."

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Insite Vision Azithromycin

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Would a claim of "room temperature up to 25°C (77°F)" be sufficient for the patient to use a product at room temperature? If it is not sufficient, what additional experiments are needed for a room temperature range of 15 °C to 30 °C?

Response: Yes it is sufficient.

3. For a refrigerated product, we assume that stability at 5°C will give us the 2°C to 8°C (36°F to 46°F) claim for storage. Would the 25°C/6 mo accelerated stability be good enough to give us the "Once opened the 2.5 ml container may be stored at room temperature up to 25°C (77°F) for X weeks" as described in the Xalatan 2°C to 8°C label?

Response: Yes. Response: Storage for un-opened bottle is adequate; but the room temperature storage condition and time for the open bottle storage would depend on the stability data of the drug product at room temperature.

4. For a marketed product intended for less than 1 week's use, is it necessary to do the simulated consumption test?

Response: Might not be necessary, if the product is stable at room temperature.

Additional notes: In preparation of the IND, please make reference to the guidance "Content and Format of Investigational New Drug application" for Phase I study. The IND submission should include a description of the drug product manufacturing process, description of the analytical method, and available stability data. The drug product specification should include particulate matter and impurities. It is also important to be sure that the drug substance is manufactured under GMP.

Preclinical

1. Is the Toxicity program sufficient to support NDA filing?

Yes, the plan is sufficient.

a) If we submit a 505 (b) (2) application, can we reference the systemic acute and sub-chronic studies from NDA 50-670 (Zithromax, Pfizer)?

Yes, a 505 b(2) application is acceptable. Pfizers NDA 50-670 application was approved in November 1991. You are required to let the holder of the original NDA know that you are submitting an application on their active ingredient.

b) Can we waive the carcinogenicity studies?

Provide justification for waiving the carcinogenicity studies to the Division.

c) Can the 14-day ocular toxicity study support clinical studies through phase II?

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Yes, if the phase 2 clinical trials go no longer than 14 days. Refer to the ICH guideline, M-3, Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals.

Additional p/t concerns: Does azithromycin bind to melanin, if so, pigmented eyes should be used in studies.

2. Is the proposed dosing regimen well supported by in vivo bioavailability data?

Response: Yes. We will review and comment on the full protocol when it is submitted.

a) Can the 1.0% ISV-401 single drop bioavailability study be initiated after IND submission?

Response: Yes.

3. Can we use the literature values on MIC values to support our label claims on in vitro susceptibility?

Response: Yes, this acceptable.

4. For those bacteria that were not cultured in clinical studies, can we reference literature and the Zithromax NDA 50-670 to support the In-Vitro microbiology section of the label?

Response: Yes, this is acceptable. As long as the bacteria are relevant to your product.

Clinical

1. The total number of subjects planned under this IND is approximately 540 subjects evaluated for safety with ISV-401 (This number includes additional subjects recruited to reach target efficacy populations in studies 002, 003, and 004). Approximately 465 subjects will receive the marketed regimen (assuming 1.0% ISV-401). Are these numbers adequate to support safety requirements for an NDA filing?

Response: Acceptable.

2. We have planned for a Phase I study of two weeks duration to support Phase II and Phase III studies with five days dosing duration (BID on Day 1 followed by QD on Days 2, 3, 4, and 5). Is that adequate from FDA's perspective?

Response: A Phase I study of two weeks duration is acceptable.

3. If a positive efficacy result is obtained with the intended marketed concentration, may our Phase II study (002) be considered as one of our two Phase III studies and replace Phase III study (003)?

Response: Potentially yes, provided the Phase 2 study is adequately powered to establish efficacy and provided the Phase 2 and Phase 3 study demonstrate replication (see Question 7).

At least one efficacy trial would need to be conducted in the United States.

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4. We plan to enroll subjects 2 years and older in Phase II and Phase III studies. Can we obtain a pediatric labeling based on this?

Response: Potentially. In order to support the drug product's eventual use in the pediatric population, approximately 10-15 subjects between the ages of 1 and 3 years of age should be exposed to azithromycin ophthalmic solution in Phase 3 trials.

5. Can pediatricians be principal investigators for bacterial conjunctivitis studies? Can a pen or flashlight be used in lieu of a slit lamp to evaluate the eye?

Response: Pediatricians can be principal investigators for bacterial conjunctivitis studies but only if an ophthalmologist serves as a subinvestigator.

Penlight and flashlight evaluations are not acceptable in lieu of slit-lamp examinations by adequately trained personnel (i.e. ophthalmologists).

6. Is gentamicin or tobramycin an acceptable positive control for Phase III studies?

Response: Yes.

7. Due to the unique dosing regimen for ISV-401, can the positive controlled Phase III study (004) be a single (investigator) masked study?

Response: No. An investigator-only masked trial design introduces the potential for unacceptable bias. Subjects will be able to unmask their treatment arm based on the differences in dosing frequency.

Options to improve the mask:

- a) use a vehicle to equalize dosing frequency; or*
- b) administer both azithromycin and active control with identical dosing frequency and establish equivalence between different azithromycin dosing regimens (with an additional study arm or in a separate trial).*

8. We plan to evaluate efficacy with [redacted] If b(4) we are successful in proving superiority to placebo and demonstrating equivalence to active, can we obtain a labeling claim with this dosing regimen?

Response: No.

9. We plan to prove superiority to placebo by demonstrating a 40% difference in microbial eradication between ISV-401 and placebo. Is this acceptable?

Response: Only if there is a clinical superiority to vehicle as well.

10. We plan to prove equivalence by demonstrating no more than a 10% difference in microbial eradication between ISV-401 and an active control. Is this acceptable?

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Response: 95% confidence interval must be within 10% for microbial equivalence but must also meet clinical equivalence.

11. Does FDA have any comment on the designs provided for the planned clinical trials?

Response: The protocols will be reviewed in their entirety when submitted to the IND, and any deficiency or problem list generated from their review will be communicated to the sponsor.

Visual acuity measurements should be obtained by age-appropriate methods, and the resulting information should be analyzed.

There will be an eventual need for a study in 0 to 1 month-olds for neonatal conjunctivitis.

All statistical tests should be two-tailed.

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/s/

Wiley Chambers
7/24/01 10:11:16 AM

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 50-810	Efficacy Supplement Type SE-	Supplement Number
Drug: Azasite (azithromycin ophthalmic solution) 1% Sterile Topical Ophthalmic Drops		Applicant: InSite Vision, Inc.
RPM: Raphael R. Rodriguez		HFD- 520 Phone # (301) 796-0798
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information that is no longer correct.</p> <p>() Confirmed and/or corrected</p>		<p>Reference Listed Drug (NDA #, Drug name): NDA 50-670 Zithromax (azithromycin) 250mg capsules</p>
❖ Application Classifications:		
• Review priority		(X) Standard () Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
• User Fee		(X) Paid UF ID number PD3006525
• User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)

❖ Application Integrity Policy (AIP)	
• 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
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug 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"/> I <input checked="" type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires.	
• [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 (certification of notification and documentation of receipt of notice). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))</i>	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
(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)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>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 next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
(3) Has the patent owner, its representative, or the exclusive patent licensee	<input type="checkbox"/> Yes <input type="checkbox"/> No

filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)). The patent owner (or its representative) may, but is not required, to provide such notification (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)?

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 next box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)). (The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2)). Note that the applicant has until the later of the following dates to provide the Division with this written notice: (a) the date marking the end of the 45-day period described in question (1), above, or (b) the date that the Division completes its review of the application (see 21 CFR 314.107(f)(2)).

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 next box below (Exclusivity).

If "Yes," a stay of approval may be in effect; answer the following questions.

- (6) (a) Was the patent subject to the paragraph IV certification submitted to FDA on or after August 18, 2003?

(Note: This can be determined by checking with [the Orange Book staff?].)

If "No," skip to question 7. If "Yes," continue with part (b).

Yes No

Yes No

Yes No

Yes No

(b) Was the patent also submitted to FDA before the date that this 505(b)(2) application was submitted as substantially complete?

If "No," there is no stay of approval based on the paragraph IV certification for this patent. If "Yes," continue with question (7).

Yes No

(7) (a) Have 30 months (or an alternate length of time ordered by the court, if any) passed from the date the patent owner received the applicant's notice of certification for the patent?

(Note: In general, approval of a 505(b)(2) application cannot be made effective (although the application can be tentatively approved) for 30 months from the date that the patent owner receives the applicant's notice of certification if a patent infringement suit is timely initiated as described in question (5) above. However, the court may order that the 30-month period be shortened or lengthened under certain circumstances. If the court has ordered that the 30-month period be altered in a particular case, the applicant is required to submit a copy of the court order to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," go to question (8). If "Yes," continue with part (b) of this question.

Yes No

(b) Before the expiration of the 30-month (or other) period described in part (a), above, did the district court hearing the patent infringement action decide whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," continue with part (c) of this question.

Yes No

(c) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

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

If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (d) of this question.

Yes No or N/A

(d) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not

infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).

If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

Yes No

- (8) (a) Has the district court hearing the patent infringement action decided whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," a stay of approval is currently in effect until the expiration of the time period described in (7)(a), above. The stay may be terminated or altered if the district court issues a decision regarding the patent's validity, enforceability, or infringement before the expiration of the time period described in (7)(a). If such a decision is issued before this time period expires, answer question (b) below.

If "Yes," continue with part (b) of this question.

Yes No

- (b) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

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

If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (c) of this question.

(c) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent.

If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).

() Yes (X) No or N/A

❖ Exclusivity (approvals only)

- Exclusivity summary Enclosed 4/27/07
- 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.)
- Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!

No

() Yes, Application # _____
(X) No

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)

General Information

❖ Actions

- Proposed action 4/27/2007
- Previous actions (specify type and date for each action taken)
- Status of advertising (approvals only)

(X) AP () TA () AE () NA

(X) Materials requested in AP letter
() Reviewed for Subpart H

❖ Public communications

- Press Office notified of action (approval only)
- Indicate what types (if any) of information dissemination are anticipated

(X) Yes () Not applicable

(X) None
() Press Release
() Talk Paper
() Dear Health Care Professional Letter

❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))

- Division's proposed labeling (only if generated after latest applicant submission of labeling)

4/13/07; 4/17/07

• Most recent applicant-proposed labeling	4/17/2007
• Original applicant-proposed labeling	6/28/2006
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DDMAC 3/23/07 DMETS 2/6/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	SEALD 7/19/06
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	4/13/07; 4/17/07
• Applicant proposed	4/16/07; 4/19/07
• Reviews	4/16/07
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	4/9/01; 1/15/03; 4/27/05;
• Pre-NDA meeting (indicate date)	6/21/05; 4/26/06
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	Enclosed
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	4/26/07
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	4/10/07
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	4/26/07
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups) Enclosed 4/27/07	one year or older has been demonstrated in controlled clinical trials
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	3/1/07; 4/26/07
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	3/19/07
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	3/12/07; 4/11/07
• Bioequivalence studies	N/A

CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	3/1/07; 4/26/07
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	Granted 3/1/07
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	4/18/07
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	2/5/07
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

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this page is the manifestation of the electronic signature.**

/s/

Raphael Rodriguez
5/3/2007 10:47:24 AM