

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-571**

**ADMINISTRATIVE DOCUMENTS AND  
CORRESPONDENCE**

Trade Name Iquix (levofloxacin ophthalmic solution 1.5%)

Generic Name levofloxacin ophthalmic solution

Applicant Name Santen HFD-550

Approval Date March 1, 2004

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

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

a) Is it an original NDA? YES/\_X\_/ NO /\_\_\_/

b) Is it an effectiveness supplement? YES /\_\_\_/ NO /\_X\_/

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 / X / 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 /\_X\_/ NO /\_\_\_/

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

3 years

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

YES /\_\_\_/ NO /\_X\_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /\_\_/  
NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /\_\_/  
NO /\_X\_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /\_X\_/ NO /\_\_/  
YES /\_\_/  
NO /\_X\_/

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

NDA # 20-634 Levaquin (levofloxacin tablet)

NDA # 20-635 Levaquin (levofloxacin injection)

NDA # 20-199 Quixin (levofloxacin ophthalmic solution) 0.5%

2. Combination product.

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

YES /\_\_\_/      NO /\_\_\_/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 /\_X\_/      NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

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

YES /  / NO /  /

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

YES /  / NO /  /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of

published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/\_/

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:

Investigation #1, Study # 16-002

Investigation #2, Study # 16-003

Investigation #3, Study #

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

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

Investigation #1 YES /\_\_\_/ NO /\_X\_/\_/

Investigation #2 YES /\_\_\_/ NO /\_X\_/\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/\_/

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

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

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

drug product?

Investigation #1                    YES /\_\_\_/                    NO /\_X\_/

Investigation #2                    YES /\_\_\_/                    NO /\_X\_/

Investigation #3                    YES /\_\_\_/                    NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

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

Investigation #\_, Study # 16-002

Investigation # , Study # 16-003

Investigation #\_\_, Study #

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 # 58,997 YES /\_X\_/    NO /\_\_\_/    Explain:

Investigation #2

IND # 58,997 YES /\_X\_/    NO /\_\_\_/    Explain:

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

Investigation #1

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

Investigation #2

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

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

YES /\_\_\_/ NO /\_X\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_

This document has been prepared by:

Lucious Lim, M.D.

Medical Officer

Date See electronic signature

Wiley A. Chambers, M.D.

Deputy Division Director

Date See electronic signature

cc:

HFD-093/Mary Ann Holovac

HFD-104/PEDES/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/

-----  
Lucious Lim  
3/1/04 02:28:50 PM

Wiley Chambers  
3/2/04 08:38:34 AM

APPEARS THIS WAY  
ON ORIGINAL

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-571 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: May 1, 2003 Action Date: March 1, 2004

HFD -550 Trade and generic names/dosage form: Iquix (levofloxacin ophthalmic solution 1.5%)

Applicant: Santen Therapeutic Class: anti-bacterial

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: treatment of corneal ulcer caused by susceptible strains of the following bacteria:

Gram-Positive Bacteria: *Corynebacterium Species\**, *Staphylococcus Aureus*, *Staphylococcus Epidermidis*,  
*Streptococcus Pneumoniae* and *Viridans* Group Streptococci\*; Gram-Negative Bacteria:  
*Pseudomonas aeruginosa* and *Serratia marcescens\**.

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:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial 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
- Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- 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
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

**Lori M. Gorski**

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-571  
HFD-960/ Grace Carmouze  
(revised 12-22-03)

**APPEARS THIS WAY  
ON ORIGINAL**

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

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

/s/

-----  
Lori Gorski  
3/1/04 02:24:22 PM

APPEARS THIS WAY  
ON ORIGINAL



DEC 16 2003

Dimitri Azar, M.D.  
Massachusetts Eye and Ear Infirmary  
243 Charles Street  
Boston, Massachusetts 02114

Dear Dr. Azar:

Between September 9 and 16, 2003, Messrs. Andrew Barlow and Robert O'Brien, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # 16-002 entitled: "A Prospective, Randomized, Parallel-Group, Multi-Center, Double-Masked Trial Comparing the Efficacy and Safety of 1.5% Levofloxacin Ophthalmic Solution with 0.3% Oxofloxacin Ophthalmic Solution for Treating Bacterial Keratitis") of the investigational drug Levofloxacin Ophthalmic Solution, performed for Santen, Incorporated. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your October, 2003 written response we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Messrs. Barlow and O'Brien presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not conduct the study according to the investigational plan [21 CFR 312.60] in that you did not obtain photographs of the study eye for 18 subjects at baseline, for 10 subjects at the follow-up visit and for 20 subjects at the confirmatory visit, as required by the investigational plan.

We acknowledge receipt of your October 10, 2003, correspondence in response to the Form FDA 483 issued September 16, 2003, outlining regulatory deficiencies found during our inspection of your clinical site. We accept your explanation and acknowledge your assurance that corrective action will be taken to prevent similar findings from occurring in any future studies.

We trust that the corrective actions you have instituted, as described in your letter, will provide adequate measures to bring your site into compliance with FDA regulations. Any response and all correspondence will be included as a permanent part of your file.

**BEST POSSIBLE COPY**

**APPEARS THIS WAY  
ON ORIGINAL**

We appreciate the cooperation shown Investigators Barlow and O'Brien during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

[ LK ]

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

APPEARS THIS WAY  
ON ORIGINAL

**BEST POSSIBLE COPY**

APPEARS THIS WAY  
ON ORIGINAL

FEI: 3004123011  
Field Classification: VAI  
Headquarters Classification:  
 X 2)VAI- no response required

Deficiencies noted:  
 X failure to adhere to protocol (05)  
Deficiency Codes: 05

cc:  
HFA-224  
HFD-550 Doc.Rm. NDA#21-571  
HFD-550 Chambers Review Div.Dir.  
HFD-550 Boyd MO  
HFD-550 Gorski PM  
HFD-46/47c/r/s/ GCP File #306  
HFD-47 Tesch  
HFR-NE250 Kravchuk DIB  
HFR-NE250 Madigan Bimo Monitor  
HFR-NE250 Barlow: O'Brien Field Investigator  
GCF-1 Seth Ray  
r/d: Tesch:11/17/03  
Reviewed: JPS:12/2/03  
f/t:ml:12/8/03

O:\Tesch\letters\azar vai letter.doc

**Reviewer Note to Rev. Div. M.O.**

This was a routine inspection of a clinical investigator. Dr. Azar's site was chosen because of high enrollment. The inspector noted two observations on the 483. The first was a failure to obtain pre-treatment, cure and confirmatory photographs of the study eye for a number of the subjects as required by the protocol. The second was the use of an informed consent with outdated IRB approval date. The consent forms for the first and second IRB approval dates were identical. This was a clerical error. Safety was not affected and this was not mentioned in the letter to the clinical investigator.

**BEST POSSIBLE COPY**

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/

-----  
Leslie Ball  
12/16/03 05:52:14 PM

APPEARS THIS WAY  
ON ORIGINAL

Food and Drug Administration  
Rockville MD 20857

John Sheppard, M.D.  
Virginia Eye Consultants  
403 Medical Tower  
Norfolk, Virginia 23507

DEC 16 2003

Dear Dr. Sheppard:

Between September 10 and 26, 2003, Mr. Stephen Eason, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol #16-002 entitled: "A Prospective, Randomized, Parallel-Group, Multi-Center, Double-Masked Trial Comparing the Efficacy and Safety of 1.5% Levofloxacin Ophthalmic Solution with 0.3% Ofloxacin Ophthalmic Solution for Treating Bacterial Keratitis") of the investigational drug 1.5% levofloxacin ophthalmic solution, performed for Santen, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Eason presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not ensure that the investigation is conducted according to the investigational plan [21 CFR 312.60].

- a. Subject 2396 did not have a pregnancy test performed prior to enrollment.
- b. Subject 2025 experienced blurred vision and difficulty opening his eye for 30 minutes after awakening on day 2 and 3 of study participation. This was not reported as an adverse event.
- c. Subjects 2503 and 2497 did not have final conjunctival specimens submitted for culture.
- d. Subject 2393 did not have culture results sent to the central lab after the local lab reported a positive test result. Subjects 2666 and 2021 had specimens sent to the central lab even though the local lab reported negative culture results.
- e. Subjects 2028, 2062, 2499, 2021, 2024, 2497, 2397, 2026, 2398, 2061, 2393, 2025, 2395, 2500, 2501, 2023, 2498 and 2502 were missing one or more of the three photographs of the study eye required by the protocol.

**BEST POSSIBLE COPY**APPEARS THIS WAY  
ON ORIGINAL

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Eason during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

[ 151 ]

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

APPEARS THIS WAY  
ON ORIGINAL

**BEST POSSIBLE COPY**

--	--	--	--	--	--

FEI: 3004123008  
Field Classification: VAI  
Headquarters Classification:  
\_\_\_1)NAI  
\_X\_2)VAI- no response required  
\_\_\_3)VAI- response requested  
\_\_\_4)OAI

Deficiencies noted:  
\_X\_ failure to adhere to protocol (05)

cc:  
HFA-224  
HFD-550 Doc.Rm. NDA#20-571  
HFD-550 Chambers Review Div.Dir.  
HFD-550 Lim MO  
HFD-550 Gorski PM  
HFD-46/47c/r/s/ GCP File #11056  
HFD-47 Tesch/Ball  
HFR-CE250 Wagner DIB  
HFR-CE250 Salisbury Bimo Monitor  
HFR-CE2535 Eason Field Investigator  
GCF-1 Seth Ray

r/d: Tesch: 12/1/03  
reviewed: LB: 12/2/03  
f/t:ml:12/8/03

O:\Tesch\letters\sheppard vai letter.doc

Reviewer Note to Rev. Div. M.O.

This was a PDUFA related inspection of Dr. John Sheppard. There were six protocol violations. All of the violations appear to have been the result of carelessness, without intent to defraud or to falsify data. A fourteen year old female subject did not have a pregnancy test done. Dr. Sheppard says he questioned her about sexual activity and was convinced a pregnancy test was not indicated. The inspector noted that one subject was enrolled with asthma. There is no evidence from the record that the asthma meets exclusion criteria for "uncontrolled chronic systemic disease". An adverse event was not reported for one subject. Two subjects did not have final specimens submitted for culture. There were minor lab problems. 70% of all subjects were missing one or more required pre and post treatment photographs. The lack of photographs has been a problem with other investigators at other sites. HFD550 is evaluating this problem.

**BEST POSSIBLE COPY**

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/

-----  
Leslie Ball  
12/16/03 05:56:54 PM

APPEARS THIS WAY  
ON ORIGINAL

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Nancy Yee, Santen Inc.

**From:** Lori Gorski, Project Manager

**Fax:** 707-254-1755

**Fax:** 301-827-2531

**Phone:** 707-256-2407

**Phone:** 301-827-2521

**Pages:** 10 (including cover page)

**Date:** November 6, 2003

**Re:** Request for clinical information # 5 on NDA 21-571

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

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

• **Comments:** Hi Nancy –

Attached is a request from the clinical reviewer for NDA 21-571, Iquix. Please respond with an amendment to the application.

1. Regarding Study 16-003: Please submit a list of all patients (patient number) included in the per protocol analysis. Please sort list by investigator number.

2. Please perform the following analyses for a modified per protocol population (MPP) for Study 16-002 and Study 16-003:

- Clinical cure at Endpoint and Endpoint with confirmation at Confirmatory Visit. Two-sided 95% CI on the cure rates also should be provided.

The patients included in the MPP for Study 16-002 are identified in attachment *NDA21571modifiedPP 16-002*. The patients included in the MPP for Study 16-003 should be the per protocol population minus the patients identified as 'Excluded from PP' in attachment *NDA21571excludePP 16-003*.

Let me know if you need clarification on anything.  
Thanks - Lori

**BEST POSSIBLE COPY**

Investigator (#)	Patient #	Treatment	Intent-to-Treat	Per Protocol	Exclude from PP
— ,077)	3001	OFLX	X		
	3002	OFLX	X		
	3003	LVFX	X		
	3004	LVFX	X		
	3005	LVFX	X		
	3006	LVFX	X		
	3007	OFLX	X		
	3008	OFLX	X		
	3009	LVFX	X		
	3010	OFLX	X		
	3011	LVFX	X		
	3012	OFLX	X		
	3013	LVFX	X		
	3014	OFLX	X		
	3015	OFLX	X		
	3016	LVFX	X		
	3017	LVFX	X		
	3018	LVFX	X		
	3019	OFLX	X		
	3020	OFLX	X		
	3021	OFLX	X		
	3022	OFLX	X		X
	3023	LVFX	X		
	3024	LVFX	X		
	3085	OFLX	X		
	3086	OFLX	X		X
	3087	LVFX	X		
	3088	LVFX	X		
	3089	OFLX	X		
	3525	OFLX	X		X
	3526	OFLX	X		
	3527	LVFX	X		X
	3528	LVFX	X		
	3529	OFLX	X		
	3530	LVFX	X		
3531	OFLX	X			
3532	LVFX	X			
3537	OFLX	X			
3538	LVFX	X			
3539	LVFX	X			
3540	OFLX	X			
3541	LVFX	X			
3542	OFLX	X			
3543	LVFX	X			
3544	OFLX	X			
3545	LVFX	X			
3546	OFLX	X			
3547	OFLX	X			
3548	LVFX	X			

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

(078)

3549	LVFX	X	
3550	LVFX	X	
3709	OFLX	X	
3025	OFLX	X	
3026	OFLX	X	
3027	LVFX	X	X
3028	LVFX	X	
3029	LVFX	X	
3030	LVFX	X	
3031	OFLX	X	
3032	OFLX	X	
3033	OFLX	X	
3034	LVFX	X	
3035	LVFX	X	
3036	OFLX	X	
3037	OFLX	X	
3038	OFLX	X	X
3039	LVFX	X	
3040	LVFX	X	
3041	OFLX	X	
3042	OFLX	X	
3043	LVFX	X	
3044	LVFX	X	
3045	OFLX	X	
3046	LVFX	X	X
3047	LVFX	X	
3048	OFLX	X	
3049	LVFX	X	
3050	LVFX	X	
3051	OFLX	X	
3052	OFLX	X	
3053	OFLX	X	X
3054	LVFX	X	
3055	OFLX	X	
3056	LVFX	X	X
3057	OFLX	X	
3058	LVFX	X	
3059	OFLX	X	
3060	LVFX	X	
3061	LVFX	X	
3062	LVFX	X	X
3063	OFLX	X	
3064	OFLX	X	X
3065	OFLX	X	
3066	LVFX	X	
3067	OFLX	X	X
3068	LVFX	X	
3069	LVFX	X	X
3070	LVFX	X	
3071	OFLX	X	
3072	OFLX	X	
3073	OFLX	X	

APPEARS THIS WAY  
ON ORIGINAL

3074	OFLX	X	
3553	LVFX	X	
3554	OFLX	X	
3555	LVFX	X	
3556	OFLX	X	
3557	LVFX	X	
3558	OFLX	X	
3559	LVFX	X	
3560	OFLX	X	
3561	LVFX	X	
3562	OFLX	X	
3563	OFLX	X	
3564	LVFX	X	
3565	OFLX	X	
3566	OFLX	X	
3567	LVFX	X	
3568	LVFX	X	
3569	OFLX	X	
3570	OFLX	X	
3571	LVFX	X	
3572	LVFX	X	X
3573	OFLX	X	
3574	LVFX	X	
3575	LVFX	X	
3576	OFLX	X	
3577	OFLX	X	X
3578	LVFX	X	X
3579	OFLX	X	
3580	LVFX	X	X
3581	LVFX	X	
3582	OFLX	X	
3583	OFLX	X	
3701	OFLX	X	
3702	LVFX	X	X
3703	LVFX	X	
3704	OFLX	X	
(079) 3501	OFLX	X	
3502	OFLX	X	
3503	LVFX	X	
(082) 3189	OFLX	X	
3509	OFLX	X	X
3510	OFLX	X	X
3511	LVFX	X	
3512	LVFX	X	X
3513	LVFX	X	X
3514	LVFX	X	X
3515	OFLX	X	X
(083) 3125	LVFX	X	X
3126	LVFX	X	X
3127	OFLX	X	X
3128	OFLX	X	X
3133	LVFX	X	X

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

	3157	LVFX	X		X
	3158	OFLX	X		X
	3159	LVFX	X		X
	3160	OFLX	X		X
	3493	LVFX	X		
	3494	OFLX	X		X
	3495	OFLX	X		
	3496	LVFX	X		
(084)	3485	LVFX	X		X
	3486	LVFX	X		X
	3487	OFLX	X		X
(085)	4001	LVFX	X		X
	4002	OFLX	X		
	4003	OFLX	X		X
	4004	LVFX	X		X
	4005	OFLX	X		
	4006	LVFX	X		
	4007	OFLX	X		X
	4008	LVFX	X		
	4081	LVFX	X		
	4082	OFLX	X		
	4083	OFLX	X		
	4084	LVFX	X		
	4085	LVFX	X		
	4086	LVFX	X		X
	4087	OFLX	X		
	4088	OFLX	X		
	4089	LVFX	X		
	4090	OFLX	X		
	4091	LVFX	X		
	4092	OFLX	X		
	4093	LVFX	X		
	4094	LVFX	X		X
	4095	OFLX	X		X
	4096	OFLX	X		
	4141	OFLX	X		X
	4142	LVFX	X		
	4243	OFLX	X		
(086)	3517	LVFX	X		X
	3518	OFLX	X		
	3519	LVFX	X		X
	3520	OFLX	X		
	3521	LVFX	X		
	3522	OFLX	X		
	3523	LVFX	X		
	3524	OFLX	X		

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

<b>Total</b>	<b>199</b>	<b>199</b>	<b>131</b>	<b>X=48</b>
	(OFLX=101)	(OFLX=101)	(OFLX=62)	(OFLX=24)
	(LVFX=98)	(LVFX=98)	(LVFX=69)	(LVFX=24)

Investigator (#)	Patient #	Treatment	Intent-to-Treat	Per Protocol	Modified Per Protocol
— (006)	2373	OFLX	X	X	
— (009)	2029	LVFX	X	X	
	2030	OFLX	X	X	X
	2031	LVFX	X		
	2032	OFLX	X	X	X
	2049	LVFX	X	X	X
	2050	LVFX	X	X	X
	2051	OFLX	X	X	X
	2052	OFLX	X		
	2441	LVFX	X		
	2442	LVFX	X	X	X
	2443	OFLX	X	X	X
	2444	OFLX	X		
— (026)	2345	LVFX	X	X	
	2346	OFLX	X		
	2347	LVFX	X		
	2701	LVFX	X	X	
	2702	LVFX	X	X	
— (035)	2133	LVFX	X	X	X
	2361	LVFX	X	X	X
	2362	LVFX	X	X	X
	2363	OFLX	X		
	2364	OFLX	X	X	X
	2633	LVFX	X		
— (038)	2053	LVFX	X		
	2054	OFLX	X	X	X
	2055	LVFX	X		
	2056	OFLX	X	X	
	2369	OFLX	X		
	2370	LVFX	X	X	
	2371	OFLX	X	X	
— (042)	2005	LVFX	X	X	X
	2006	LVFX	X		
	2007	OFLX	X	X	X
	2008	OFLX	X		
	2037	LVFX	X	X	X
	2038	OFLX	X	X	X
	2039	OFLX	X		
	2378	LVFX	X	X	X
— (049)	2089	OFLX	X	X	X
	2090	OFLX	X	X	
	2091	LVFX	X	X	X
	2437	LVFX	X		
	2438	LVFX	X	X	X
	2439	OFLX	X		
→ (059)	2001	LVFX	X	X	X
	2002	OFLX	X	X	
	2003	LVFX	X		
	2004	OFLX	X	X	
	2105	OFLX	X		

	2106	OFLX	X			page 2
	2385	LVFX	X	X		
(064)	2333	LVFX	X			
	2334	LVFX	X	X	X	
	2335	OFLX	X			
	2336	OFLX	X	X	X	
	2529	OFLX	X			
	2530	OFLX	X			
	2531	LVFX	X			
	2532	LVFX	X	X	X	
	2605	LVFX	X	X		
	2606	LVFX	X	X	X	
	2607	OFLX	X			
	2608	OFLX	X			
	2709	OFLX	X			
Azar (065)	2113	LVFX	X			
	2114	LVFX	X	X		
	2115	OFLX	X			
	2341	OFLX	X			
	2342	OFLX	X	X		
	2343	LVFX	X	X		
	2344	LVFX	X			
	2449	LVFX	X			
	2450	OFLX	X	X		
	2451	LVFX	X	X		
	2452	OFLX	X	X		
	2453	OFLX	X	X	X	
	2454	OFLX	X	X		
	2455	LVFX	X			
	2456	LVFX	X			
	2473	LVFX	X	X		
	2474	OFLX	X	X		
	2475	LVFX	X			
	2476	OFLX	X	X		
	2477	LVFX	X			
	2478	LVFX	X			
	2561	OFLX	X	X		
	2562	OFLX	X	X		
	2613	LVFX	X	X		
	2614	OFLX	X	X		
(066)	2013	OFLX	X	X	X	
	2014	OFLX	X	X		
	2015	LVFX	X	X		
(068)	2077	LVFX	X	X	X	
	2078	OFLX	X	X		
	2349	OFLX	X	X	X	
	2351	LVFX	X	X		
	2621	LVFX	X	X		
	2622	OFLX	X	X	X	
Sheppard (070)	2021	LVFX	X	X	X	
	2022	LVFX	X			
	2023	OFLX	X			

	2024	OFLX	X	X	X	page 3
	2025	LVFX	X			
	2026	OFLX	X			
	2027	LVFX	X			
	2028	OFLX	X			
	2061	LVFX	X			
	2062	LVFX	X	X	X	
	2393	OFLX	X	X	X	
	2394	OFLX	X	X	X	
	2395	LVFX	X			
	2396	LVFX	X			
	2397	LVFX	X			
	2398	LVFX	X			
	2399	OFLX	X			
	2400	OFLX	X	X	X	
	2497	LVFX	X	X	X	
	2498	OFLX	X	X		
	2499	LVFX	X			
	2500	OFLX	X			
	2501	LVFX	X	X		
	2502	LVFX	X			
	2503	OFLX	X			
	2665	LVFX	X	X	X	
	2666	LVFX	X	X	X	
	2667	OFLX	X			
—	(071)	2073	OFLX	X		
		2405	OFLX	X		
		2406	LVFX	X		
		2661	OFLX	X	X	
		2662	OFLX	X	X	
—	(072)	2101	LVFX	X	X	
		2102	OFLX	X		
		2103	LVFX	X		
		2104	OFLX	X		
		2125	LVFX	X	X	
		2126	LVFX	X	X	
		2409	LVFX	X		
		2410	LVFX	X	X	
		2411	OFLX	X		
—	(073)	2057	LVFX	X	X	
		2058	OFLX	X		
		2417	OFLX	X	X	
		2418	OFLX	X	X	
—	(075)	2041	LVFX	X		
		2042	LVFX	X		
		2043	OFLX	X		
		2044	OFLX	X		
		2149	OFLX	X		
		2150	LVFX	X	X	
		2429	OFLX	X	X	
		2430	LVFX	X		
		2431	LVFX	X		

	2705	OFLX	X	X	X	page 4
— (080)	2045	OFLX	X	X	X	
	2046	LVFX	X	X	X	
	2047	LVFX	X	X		
	2337	LVFX	X	X		
	2338	OFLX	X	X	X	
	2339	OFLX	X	X	X	
	2340	LVFX	X			
	2517	LVFX	X	X		
	2518	LVFX	X			
	2609	OFLX	X			
	2610	LVFX	X	X		
— (081)	2033	OFLX	X			
	2034	LVFX	X			
	2357	LVFX	X			
	2358	LVFX	X	X		
	2359	OFLX	X	X		
	2360	OFLX	X	X		
	2485	OFLX	X			
	2486	OFLX	X			
	2487	LVFX	X			
— (087)	2421	OFLX	X			
	2422	OFLX	X			
	2423	LVFX	X	X	X	
	2673	OFLX	X			
	2674	OFLX	X			
— (088)	2457	OFLX	X			
	2458	OFLX	X	X		
	2459	LVFX	X	X		
	2460	LVFX	X	X		
— (089)	2353	LVFX	X	X		
— (095)	2461	LVFX	X			
	2462	LVFX	X	X		
	2463	OFLX	X			
	2464	OFLX	X	X		
— (096)	2481	LVFX	X			
	2482	OFLX	X	X	X	
	2483	LVFX	X	X	X	
	2484	OFLX	X			
	2489	OFLX	X			
— (097)	2549	OFLX	X	X		
	5001	LVFX	X	X	X	
	5002	OFLX	X	X		
	5003	OFLX	X	X		
	5004	LVFX	X	X	X	
	5037	LVFX	X	X	X	
	5038	LVFX	X	X	X	
— (101)	6009	LVFX	X	X		
	6010	OFLX	X	X	X	
	6011	OFLX	X	X		
	6049	OFLX	X	X		
	6050	OFLX	X	X	X	

	6051	LVFX	X	X	X	page 5
	6052	LVFX	X			
	6053	OFLX	X	X		
	6054	OFLX	X	X		
	6055	LVFX	X	X		
-	(102)	6001	OFLX	X		
		6002	LVFX	X	X	
		6003	OFLX	X		
		6004	LVFX	X	X	
		6005	LVFX	X	X	
		6006	LVFX	X	X	
		6045	LVFX	X	X	
		6046	OFLX	X	X	
		6047	LVFX	X	X	
		6048	OFLX	X	X	
		6057	OFLX	X	X	
		6058	LVFX	X	X	X
		6059	LVFX	X	X	
		6060	OFLX	X	X	
		6061	LVFX	X	X	
		6062	LVFX	X	X	X
		6063	OFLX	X	X	
		6064	OFLX	X	X	
		6065	OFLX	X	X	X
		6066	LVFX	X	X	
		6067	OFLX	X	X	
		6068	LVFX	X	X	
		6077	LVFX	X	X	
		6078	LVFX	X		
-	(104)	2521	LVFX	X		
		2629	OFLX	X		
<b>Total</b>	<b>237</b>		<b>237</b>	<b>X=149</b>	<b>X=72</b>	
			<b>(OFLX=116)</b>	<b>(OFLX=71)</b>	<b>(OFLX=31)</b>	
			<b>(LVFX=121)</b>	<b>(LVFX=78)</b>	<b>(LVFX=41)</b>	

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/  
-----

Lori Gorski  
11/7/03 09:25:03 AM  
CSO

Lori Gorski  
11/7/03 09:28:54 AM  
CSO  
faxed to the sponsor 11/6/03

APPEARS THIS WAY  
ON ORIGINAL

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Nancy Yee, Santen Inc.

**From:** Lori Gorski, Project Manager

**Fax:** 707-254-1755

**Fax:** 301-827-2531

**Phone:** 707-256-2407

**Phone:** 301-827-2521

**Pages:** 1 (including cover page)

**Date:** October 27, 2003

**Re:** Request for clinical information # 4 on NDA 21-571

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

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

● **Comments:**

Hi Nancy –

Attached is a request from the clinical reviewer for NDA 21-571, Iquix. Please respond with an amendment to the application.

Study 16-002: Please submit a list of all patients (patient number) included in the per protocol analysis. Please sort list by investigator number.

Let me know if you need clarification on anything.

Thanks

Lori

**BEST POSSIBLE COPY**

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

/s/  
-----

Lori Gorski  
10/27/03 11:45:59 AM  
CSO

Lori Gorski  
10/27/03 11:47:54 AM  
CSO  
faxed to sponsor 10/27/03

APPEARS THIS WAY  
ON ORIGINAL

**CONSULTATION RESPONSE**  
**Division of Medication Errors and Technical Support**  
**Office of Drug Safety**  
**(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> May 14, 2003	<b>DESIRED COMPLETION DATE:</b> July 14, 2003 <b>PDUFA DATE:</b> March 1, 2004	<b>ODS CONSULTS #:</b> 03-0165
---------------------------------------	---	-----------------------------------

**TO:** Lee Simon, MD  
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products  
HFD-550

**THROUGH:** Lori Gorski  
Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products  
HFD-550

<b>PRODUCT NAME:</b> Iquix (Levofloxacin Ophthalmic Solution) 1.5%	<b>NDA SPONSOR:</b> Santen Incorporated
---	--

**NDA # 21-571**

**SAFETY EVALUATOR:** Scott Dallas, R.Ph.

**SUMMARY:** In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "Iquix", to determine the potential for confusion with approved proprietary and established names as well as pending names. The proposed container labels, carton and package insert labeling were reviewed in an attempt to focus on safety issues to prevent possible medication errors.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, "Iquix".
2. DMETS recommends implementation of the labeling revisions outlined in Section III to encourage the safest possible use of this product.
3. DDMAC finds the name Iquix acceptable from a promotional perspective.

---

Carol Holquist, RPh  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax (301) 443-9664

---

Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Parklawn Building Room 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 24, 2003  
NDA NUMBER: 21- 571  
NAME OF DRUG: Iquix  
(Levofloxacin Ophthalmic Solution)  
1.5%  
NDA SPONSOR: Santen Incorporated

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) for an assessment of the proposed proprietary name Iquix. The container labels, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The assessment of the proposed name, Iquix, is for a levofloxacin ophthalmic solution 1.5% product. The sponsor is currently marketing a levofloxacin ophthalmic solution 0.5% product using the tradename Quixin. The levofloxacin ophthalmic solution 0.5% product was approved August 18, 2000, NDA# 21-199.

PRODUCT INFORMATION

Iquix is the proposed name for a sterile topical ophthalmic solution. The ophthalmic solution contains the fluoroquinolone antibacterial agent levofloxacin. The ophthalmic solution is indicated for the treatment of corneal ulcer caused by susceptible strains of bacteria. The product will be available as levofloxacin ophthalmic solution 1.5% in a 5 mL container.

APPEARS THIS WAY  
ON ORIGINAL

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>\*\*\*</sup>,<sup>†††</sup> as well as several FDA databases<sup>†††</sup> for existing drug names which sound-alike or look-alike to "Iquix" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted<sup>§§§</sup>. The Saegis<sup>\*\*\*\*</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Iquix". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two proprietary names and one proposed name that have the potential for confusion with "Iquix". These products are listed in Table 1 (refer to page 4), along with the dosage forms available and usual dosage.
2. DDMAC did not have any concerns with the promotional aspects of the name, "Iquix".

APPEARS THIS WAY  
ON ORIGINAL

---

<sup>1</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/main/trademarks.htm>

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

TABLE 1

Product Name	Generic name, Dosage form(s), and Strength(s)	Indication for use and Usual adult dose*	Other**
Iquix	Levofloxacin, Ophthalmic Solution, 1.5%	Indicated for the treatment of corneal ulcer caused by susceptible strains of bacteria. Usual dose:	
Oraqix***	Lidocaine and Prilocaine, Peridental Gel, 2.5%/2.5%	Indicated for localized anesthesia  Usual dose: Instill 1 cartridge or less for one quadrant of dentition.	S/A per DMETS
Lasix	Furosemide, Tablet, 20 mg, 40 mg, and 80 mg, Oral Solution, 10 mg/mL, Injection, 10 mg/mL	Indicated for the treatment of edema and hypertension, alone or with other antihypertensive medications. Usual dose for edema: Take 20 mg to 80 mg once daily. Usual dose for hypertension: Take 40 mg twice a day.	S/A per DMETS
Hiprex	Methenamine Hippurate, Tablet, 1 gram	Indicated for the prophylaxis or suppression/elimination of frequently recurring urinary tract infections. Usual dose: Take one tablet twice daily.	S/A per DMETS

\* Frequently used, not all-inclusive. \*\* L/A (look-alike), S/A (sound-alike) \*\*\* Pending Approval – Proprietary and confidential information that should not be released to the public.

## B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

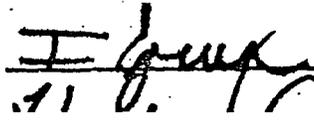
DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

## C. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology for Iquix Studies

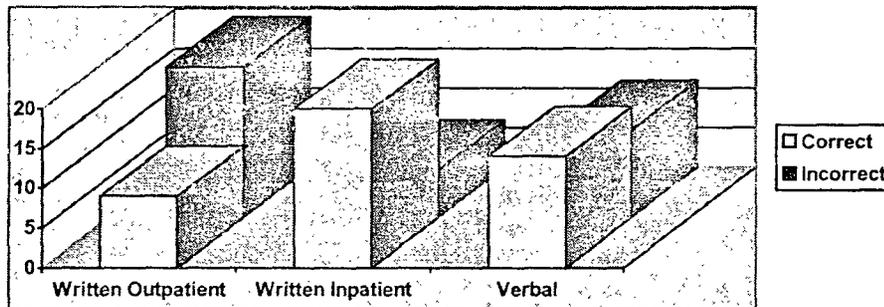
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Iquix with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 128 health care professionals (nurses, pharmacists, and physicians) for Iquix. This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Iquix. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

Iquix Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Outpatient:</p> 	<p>Outpatient:</p> <p>Iquix Sig: one drop left eye every 2 hours while awake and repeat 4 hours after bedtime. Dispense 1</p>
<p>Inpatient:</p> 	

2. Results of the Iquix Studies

Study	Number of participants	Number of responses (%)	"Iquix" responses (%)	Other responses (%)
Written: Outpatient	43	28 (65%)	9 (32%)	19 (68%)
Inpatient	42	26 (62%)	20 (77%)	6 (23%)
Verbal: Outpatient	43	25 (58%)	14 (56%)	11 (44%)
Total:	128	79 (67%)	43 (54%)	36 (46%)



Among participants in the written outpatient prescription study, 9 of 28 respondents (32%) interpreted the name correctly. Incorrect interpretations included Quix (2), Clarix (1), Clegoix (1), Clovix (1), Clquix (1), Dguix (1), Digoix (1), Dorix (1), Dovix (1), Dquix (5), Lasix (1), Igix (1), Iqix (1), and Olquix (1).

Among participants in the written inpatient prescription study, 20 of 26 respondents (77%) interpreted the name correctly. Incorrect interpretations included Igix (2), Iguix (1), Iguix (1), and Iguix (2).

Among participants in the verbal outpatient prescription study, 14 of 25 respondents (56%) interpreted the name correctly. Incorrect interpretations included Eyefix (1), Eyequick (1), Eyequicks (2), Eyequix (4), Iquick (1), Iquicks (1), and Iquirks (1).

One respondent in the written outpatient prescription study interpreted the name as Lasix, a currently marketed drug product. Another respondent commented the name could be interpreted as Plavix or Lasix. Plavix is also a currently marketed drug product. It is also interesting to note that 8 respondents in the verbal outpatient prescription study interpreted the letter "l" sound as "eye".

#### D. SAFETY EVALUATOR RISK ASSESSMENT

**\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

The sponsor is currently marketing this active ingredient, levofloxacin, under the proprietary name Quixin, NDA 21-199. This levofloxacin ophthalmic solution differs only in the product strength and indication for use. Following numerous discussions with the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, it is our understanding ophthalmic products that differ in product strength or indications for use are different drug products, and thus require a new proprietary name. DMETS doesn't believe that it is absolutely necessary to have two proprietary names because of different strengths and indications. FDA has an ample number of drug products approved under these conditions and are safely prescribed and dispensed under one proprietary name. However, in this case, DMETS does not envision potential name confusion between Iquix and Quixin, nor can we envision scenarios where Iquix and Quixin would be concomitantly prescribed, or pose a significant safety risk as a result of concomitant usage.

However, when evaluating the proprietary name "Iquix", three names were identified with potential sound-alike characteristics to Iquix. Two names were proprietary names that already exist in the U.S. marketplace and one name was a proposed name that is pending approval. The names considered having the greatest potential for confusion with "Iquix" were Lasix, Oraqix<sup>\*\*\*</sup>, and Hiprex.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Iquix could be confused with Lasix, when one respondent in the written prescription study interpreted the name as Lasix. Although there are limitations to the predictive value of this study, primarily due to the sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Lasix and the proposed name, Iquix have the potential to sound similar when spoken. The last syllable of each name is phonetically similar when pronounced, "ix vs. quix". However, these medications have differentiating characteristics. Lasix and Iquix have different product strengths (20 mg, 40 mg, 80 mg, and 10 mg/mL vs. 1.5%), indication for use (treatment of edema and hypertension vs. treatment of corneal ulcers), unit of measure (tablet or mL vs. drop), route of administration (oral

---

<sup>\*\*\*</sup> Pending Approval – Proprietary and confidential information that should not be released to the public.

or parenteral vs. topical), and frequency of administration (once a day or twice a day vs. every 2 hours or 4 times a day while awake). The different characteristics of the medications should decrease the potential risk of a medication error involving these two products.

2. Oraqix and the proposed name, Iquix have the potential to sound similar when spoken. The last syllable of each name is phonetically similar when pronounced, "qix vs. quix". However, these medications have differentiating characteristics. Oraqix and Iquix have different product strengths (2.5%/2.5% vs. 1.5%), container size (1.7 gram vs. 5 mL), package configuration (cartridge vs. bottle), indication for use (anesthesia during dental procedures vs. treatment of corneal ulcers), usual dose (apply contents of cartridge vs. 1 to 2 drops), and frequency of administration (during dental procedure vs. \_\_\_\_\_). Oraqix is intended to be applied by a trained healthcare professional via a \_\_\_\_\_ in a dental office setting. It is not intended for Oraqix to be dispensed to the general public. The different characteristics of the medications should decrease the potential risk of a medication error involving these two products.
3. Hiprex and the proposed name, Iquix have the potential to sound similar when spoken. The last syllable of each name can sound similar when pronounced, "rex vs. quix". However, these medications have differentiating characteristics. Hiprex and Iquix have different product strengths (1 gram vs. 1.5%), indication for use (prophylaxis of urinary tract infections vs. treatment of corneal ulcers), unit of measure (gram vs. drop), route of administration (oral vs. topical), dosage formulation (tablet vs. solution) and frequency of administration (twice a day vs. every 2 hours or 4 times a day while awake). The different characteristics of the medications should decrease the potential risk of a medication error involving these two products.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS reviewed the container labels, carton and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. The container labels and carton labeling were presented in black and white, therefore DMETS cannot assess if there are any safety issues due to the use of colors. DMETS has identified the following areas of possible improvement in the interest of minimizing user error and maximizing patient safety.

#### A. General Comment:

1. To decrease the likelihood of a product selection error, DMETS recommends the container labels and carton labeling for levofloxacin ophthalmic solution 1.5% is clearly differentiated from the container labels and carton labeling for levofloxacin ophthalmic solution 0.5%.
2. DMETS recommends increasing the prominence of the proprietary and established names, and product strength on the container labels and carton labeling.

#### B. Container Label (\_\_\_\_\_ 5mL)

1. See General Comments.
2. DMETS recommends decreasing the prominence of the company logo "Santen" and round image on the principal display panel. This distracts from the important information, such as the name and the strength of the drug product.
3. Relocate the route of administration to the principal display panel.

C. Carton Labeling (1mL and 5mL)

1. See General Comments.
2. See comments 2A and 2B above.

**IV. RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, "Iquix".
2. DMETS recommends implementation of the labeling revisions outlined in Section III to encourage the safest possible use of this product.
3. DDMAC finds the name, Iquix, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

---

Scott Dallas, R.Ph.  
Safety Evaluator  
Office of Drug Safety (DMETS)

Concur:

---

Denise Toyer, Pharm.D.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

**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.  
-----

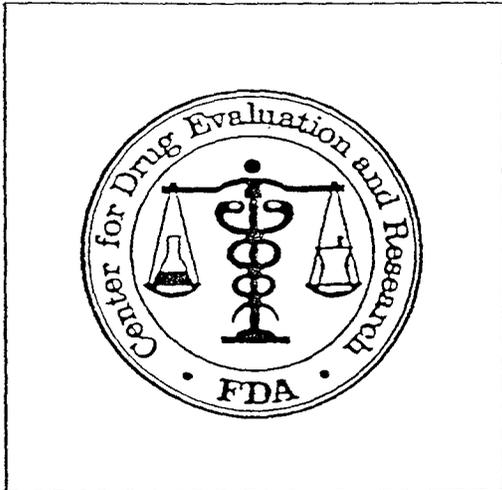
/s/

-----  
Carol Holquist  
10/24/03 08:13:51 PM  
DRUG SAFETY OFFICE REVIEWER

APPEARS THIS WAY  
ON ORIGINAL

*Hossein Shawn*

FACSIMILE TRANSMISSION  
RECORD



From: Hossein Shawn Khorshidi, Ph.D.

Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2040  
Fax 301-827-2531

Date: 9/26/03

To: Name Lisa Ann Suchar, Director  
Company Santien Inc Regulatory Affairs  
City Napa state CA  
Phone # (707) 256-2473  
FAX # (707) 254-1755

Number of Pages (INCLUDING COVER PAGE) 1 + 2 = 3

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

**THIS DOCUMENT IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND  
MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM  
DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any view, disclosure, copying, or other action based on the content of this communication is NOT authorized. If you have received this document in error, please notify us immediately by telephone and return it to us at the above address by mail. Thank you.

Additional message:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

September 26, 2003

NDA 21-571

Iquix™ (levofloxacin ophthalmic solution) 1.5%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

*Drug product:*

1. In the drug product specification, the proposed acceptance criteria for the \_\_\_\_\_ total impurities and osmolality are not acceptable. Based on data, the following acceptance criteria are proposed:

_____	NMT _____
Total impurities:	NMT _____
Osmolality:	_____

2. Submitted stability data do not support the proposed expiration-dating period of \_\_\_\_\_ and 24 months for the \_\_\_\_\_ 5ml fill/5 cc LDPE bottles. Based on data, we recommend the expiration-dating period of \_\_\_\_\_ and \_\_\_\_\_ for \_\_\_\_\_ 5ml fill/5 cc bottles respectively. Alternatively, to consider the proposed expiry of 24 months (for the 5ml fill size bottles), you can submit the statistical analysis and the shelf life projection data for the registration batches.

cc:

NDA 21-571, Div. File  
HFD-550, L. Ng  
HFD-550, W. Chambers  
HFD-550, L. Gorski

APPEARS THIS WAY  
ON ORIGINAL

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Nancy Yee, Santen Inc.

**From:** Lori Gorski, Project Manager

**Fax:** 707-254-1755

**Fax:** 301-827-2531

**Phone:** 707-256-2407

**Phone:** 301-827-2521

**Pages:** 1 (including cover page)

**Date:** August 28, 2003

**Re:** Request for clinical information # 3 on NDA 21-571

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

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

● **Comments:**

Hi Nancy –

Attached is a request from the clinical reviewer for NDA 21-571, Iquix. Please respond with an amendment to the application.

Study 16-001: Section 14.3.4 (NDA page M5-V01-037) states that “Complete visual acuity information for each subject is presented in Appendix 18.2.13 (NDA page M5-V01-364). The information referred to in Section 14.3.4 are not contained in Appendix 18.2.13. Please identify the location where the complete visual acuity information may be found.

Let me know if you need clarification on anything.

Thanks

Lori

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

/s/  
-----

Lori Gorski  
8/28/03 04:48:56 PM  
CSO

Lori Gorski  
8/28/03 04:50:58 PM  
CSO  
faxed to sponsor 8/28/03

APPEARS THIS WAY  
ON ORIGINAL

2 Page(s) Withheld



**FILING REVIEW LETTER**

NDA 21-571

Santen Incorporated  
Attention: Nancy Yee  
Regulatory Affairs Specialist II  
555 Gateway Drive  
Napa, California 94558

Dear Ms. Yee:

Please refer to your April 30, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iquix (levofloxacin ophthalmic solution), 1.5%

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 30, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following review issue:

The application lacks information necessary to evaluate the [redacted] items not provided include procedures, specifications and results for [redacted] validation and the [redacted]. This information should be provided promptly to this Division for review.

We are providing the above comments to give you preliminary notice of review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

**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  
6/27/03 03:29:05 PM

APPEARS THIS WAY  
ON ORIGINAL

MEMORANDUM

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

---

DATE: May 15, 2003

TO: IND 58,997  
Levofloxacin ophthalmic solution 1.5%  
Sponsor: Santen Incorporated

FROM: Peter A. Dionne  
Microbiologist  
Division of Special Pathogen and Immunologic Drug Products (DSPIDP)

THROUGH: Shukal Bala, Ph.D.  
Microbiology Team Leader  
Division of Special Pathogen and Immunologic Drug Products (DSPIDP)

SUBJECT: IQUIX® (levofloxacin ophthalmic solution) 1.5% label

I have reviewed the microbiology section of the IQUIX label and have a few comments. This label basically follows the QUIXIN (levofloxacin ophthalmic solution) 0.5% label. My comments follow:

1. In the first paragraph of the Microbiology section, the sentence that begins "The mechanism of action of levofloxacin..." has the words "and other fluoroquinolone antimicrobials" deleted from what is in the QUIXIN label. In order to be consistent these words should be added. The sentence should read "The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves the inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair, and recombination."
2. In list #1 (clinical efficacy shown) *Staphylococcus aureus* and *Staphylococcus epidermidis* should be listed as *Staphylococcus aureus* and *Staphylococcus epidermidis*

3. The following species have been added to the IQIIX label (clinical efficacy listing) which are not in the QUIXIN: \_\_\_\_\_; *Pseudomonas aeruginosa*, \_\_\_\_\_ . These species may be added to the label if they are allowed in the Indication. *Pseudomonas aeruginosa* is listed in the *in vitro* activity section of the QUIXIN label and is in the levofloxacin systemic (table and IV) label.

4. The *in vitro* activity listing (list #2) is identical to that in the QUIXIN label. I have the following comments:

- *Enterococcus faecalis* should be listed as *Enterococcus faecalis* (many strains are only moderately susceptible). This is the way it is listed in the systemic label since levofloxacin's MIC<sub>90</sub> value is higher than the susceptible breakpoint. The QUIXIN label has this species listed as just *Enterococcus faecalis* without the qualifying statement.
- \_\_\_\_\_ should be deleted. This species has been reclassified and is not longer in the systemic label.
- \_\_\_\_\_ has been reclassified as \_\_\_\_\_
- \_\_\_\_\_ has been reclassified as *Pantoea agglomerans*
- \_\_\_\_\_
- *Streptococcus* (Group C/F), *Streptococcus* (Group G), *Haemophilus influenzae*, and *Acinetobacter lwoffii* may be added to this listing in alphabetical order in the appropriate section. These organisms are in the clinical efficacy listing in the QUIXIN label and levofloxacin has *in vitro* activity against them.

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/  
-----

Lori Gorski  
12/5/03 03:08:15 PM  
CSO

Lori Gorski  
12/5/03 03:10:11 PM  
CSO  
faxed to sponsor 12/5/03

APPEARS THIS WAY  
ON ORIGINAL

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Nancy Yee, Santen Inc.

**From:** Lori Gorski, Project Manager

**Fax:** 707-254-1755

**Fax:** 301-827-2531

**Phone:** 707-256-2407

**Phone:** 301-827-2521

**Pages:** 1 (including cover page)

**Date:** June 27, 2003

**Re:** Request for clinical information # 2 on NDA 21-571

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

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

• **Comments:**

Hi Nancy –

Attached is a request from the clinical reviewer for NDA 21-571, Iquix. Please respond with an amendment to the application.

Please provide the visual acuity safety data and analysis for Studies 16-001, 16-002, 16-003, and 16-006 in the following format. Alternatively, if this information is included in the original submission, please identify the location.

1. Change in visual acuity from baseline to final visit/confirmatory visit by number of line(s) change (i.e.,  $\geq 2$  lines loss, 1 line loss, no change, 1 line gain,  $\geq 2$  lines gain) for each treatment group.

Let me know if you need clarification on anything.

Thanks

Lori

**BEST POSSIBLE COPY**

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

/s/  
-----

Lori Gorski  
6/27/03 04:12:29 PM  
CSO

Lori Gorski  
6/27/03 04:14:14 PM  
CSO  
faxed to sponsor 6/27/03

APPEARS THIS WAY  
ON ORIGINAL

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Nancy Yee, Santen Inc.

**From:** Lori Gorski, Project Manager

**Fax:** 707-254-1755

**Fax:** 301-827-2531

**Phone:** 707-256-2407

**Phone:** 301-827-2521

**Pages:** 1 (including cover page)

**Date:** June 20, 2003

**Re:** Request for clinical information on NDA 21-571

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

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

● **Comments:**

Hi Nancy – Attached is a request from the reviewers for NDA 21-571, Iquix. Please respond with an amendment to the application.

Please identify where the following information/analyses for the intent-to-treat (ITT) and per protocol (PP) populations are located in the submission. If they are not included in the submission, please submit them:

1. Clinical cure at Endpoint with confirmation at Confirmatory Visit for both treatment groups. Two-sided 95% CI on the cure rates also should be provided.
2. Clinical cure at Endpoint and Endpoint with confirmation at Confirmatory Visit grouped by epithelial defect size at baseline (in 0.5 mm<sup>2</sup> increment. E.g., >0.0-0.5, >0.5-1.0, >1.0-1.5, etc.) for both treatment groups. Two-sided 95% CI on the cure rates also should be provided.

Please resubmit summary.xpt with the clinical cure endpoint as described in item 1. Please also submit the data formats associated with efficacy.xpt and summary.xpt.

Let me know if you need clarification on anything. - Thanks  
Lori

**BEST POSSIBLE COPY**

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

/s/

-----  
Lori Gorski  
6/20/03 10:26:19 AM  
CSO

Lori Gorski  
6/20/03 10:27:50 AM  
CSO  
fax sent to sponsor on 6/20/03

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-571

Santen Incorporated  
Attention: Nancy Yee  
Regulatory Affairs Specialist II  
555 Gateway Drive  
Napa, California 94558

Dear Ms. Yee:

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

Name of Drug Product: Iquix (levofloxacin ophthalmic solution), 1.5%

Review Classification: Standard (S)

Date of Application: April 30, 2003

Date of Receipt: May 1, 2003

Our Reference Number: NDA 21-571

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 29, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 1, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
9201 Corporate Boulevard  
Rockville, Maryland 20850

NDA 21-571

Page 2

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/  
-----

Lori Gorski  
5/12/03 09:50:54 AM  
Lori Gorski has signed for Carmen DeBellas

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 58,997

Santen Incorporated  
Attention: Nancy S. Yee  
Regulatory Affairs Specialist II  
555 Gateway Drive  
Napa, California 94558

Dear Ms. Yee:

Please refer to your submission date January 10, 2003, requesting a waiver for pediatric studies for levofloxacin ophthalmic solution, 1.5 %.

The Pediatric Final Rule (21 CFR Parts 201, 312, 314 and 601; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule) is no longer in effect and therefore the provision in the regulation allowing the FDA to grant or deny waivers no longer exists.

The FDA still encourages sponsors to conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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  
4/17/03 10:07:00 AM

APPEARS THIS WAY  
ON ORIGINAL

2

\_\_\_\_\_ Page(s) Withheld

## MEETING MINUTES

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

**MEETING DATE:** November 13, 2002

**TIME:** 11:30 AM EST

**Pre-NDA:** 58,997

**DRUG:** Levofloxacin ophthalmic solution 1.5%

**Meeting Request Date:** September 5, 2002

**Date Sponsor Requested:** November 13, 2002

**Briefing Document Submission Date:** October 14, 2002

**SPONSOR/APPLICANT:** Santen

**MEETING TYPE:** Pre-NDA meeting - application due in March 2003.

### FDA PARTICIPANTS:

Lori Gorski, Project Manager  
Wiley Chambers, Deputy Director  
Bill Boyd, Medical Officer  
Jennifer Harris, Medical Officer  
Lucious Lim, Medical Officer  
Matt Feinsod, Medical Officer  
Raphael Rodriguez, Project Manager  
Mike Puglisi, Project Manager  
Allan Fenselau, Chemistry Reviewer  
Linda Ng, Chemistry Team Leader  
Vinnie Pawar, Microbiology Reviewer  
Josie Yang, Pharm/Tox Team Leader  
Laura Lu, Biostat Reviewer  
Carmen Debellas, Supv CSO  
Lee Simon, Division Director  
Jonca Bull, ODE5 Director

### List of Santen Participants

Jeff Wells, Pharm D, MBA; VP, Clinical Affairs, RA, and PM  
Gary Krasner, PhD; Manager, Clinical Affairs  
Mark Holdbrook, BA; Director, Biostatistics  
Shawn Hickok, BS; Director, Formulations and Technology Transfer  
Leslie Clark, DVM; Director, Preclinical Development  
Lisa Ann Suchar, PhD; Director, Regulatory Affairs  
Nancy Yee, MS; Regulatory Affairs Specialist II  
Consultant

**MEETING OBJECTIVES:** To gain additional guidance in preparation of the NDA submission for March 2003.

**BACKGROUND INFORMATION:** This application for 1.5% levofloxacin ophthalmic for the indication of \_\_\_\_\_ The NDA will cross-reference Santen's approved NDA 21-199 for QUIXIN™(levofloxacin ophthalmic solution) 0.5%, approved 18 August 2000 for the treatment of bacterial conjunctivitis. It will be filed in a modified CTD format.

### Items for Discussion - Clinical

1. Santen proposes the following labeled dosing regimen:

Does the agency agree that the design of our studies conducted supports this dosing regimen?

**FDA Response:** *Labeled dosing regimen is a review issue. A decision on final labeling will need to come after review of the NDA.*

2. Santen proposes to include in the 1.5% levofloxacin ophthalmic solution labeling

[

7

L

-1

Does the agency agree with this proposal?

**FDA Response:** *No.* [

3

[

]

//

/

2  
7y

#### Quality (Chemistry, Manufacturing, and Controls)

4. Please confirm the acceptability of the proposed drug product specifications.

**FDA Response:** *The acceptance criteria for Levofloxacin Related Substances, Osmolality, and pH will be based on results from stability studies. As stated, "Other individual impurities" at NMT — will not be acceptable. The specification should list "Specified unknown impurities" with acceptance criteria determined from stability studies and "Any individual unspecified impurity" at NMT — The unknown impurities can be specified in terms of a relative retention time.*

5. Santen is planning to submit the following stability data package in the NDA:

— on — of the 5 mL fill size

/

Is this plan acceptable to the agency?

**FDA Response:** *Yes. It is also understood that — of accelerated stability data, including — will be provided for — lots.*

6. Because US Federal Standard 209E was withdrawn November 2001 and replaced by ISO 14644-1 and 14644-2, how would the agency like to see room classifications presented in the NDA?

**FDA Response:** *Yes, it is acceptable to provide the ISO information. It is recommended that the sponsor provide similar data with regard to \_\_\_\_\_ s was submitted in the Quixen application.*

#### **Administrative**

7. Does the agency have any comments on the proposed labeling at this time?

**FDA Response:** *No. A decision on final labeling will need to come after review of the NDA.*

8. Please comment on the draft NDA table of contents.

**FDA Response:** *Acceptable.*

9. Santen intends on providing the archival copy of the NDA electronically in Portable Document Format (ADOBE ACROBAT), including in-text hyperlinks, and the review copies as paper. Is this acceptable to the agency?

**FDA Response:** *Acceptable. 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*

10. Santen would like to submit all case report form tabulations electronically but not include them in the review copies of the submission. Will the agency please comment on the acceptability of this strategy?

**FDA Response:** *Acceptable.*

11. Would the agency like Santen to provide analysis datasets for our Phase III studies?

**FDA Response:** *Yes.*

12. We would like to propose the following pagination scheme for the submission, which will be in CTD format:

**Modules 1, 3, 4, and 5:** Each module paginated from 1 to N

**FDA Response:** *Acceptable.*

**Module 2:** Each section paginated from 1 to N

**FDA Response:** *Pagination of Module 2 (the entire Chemistry Section) from 1 to N is preferred. Overall, the volumes within every section should be numbered.*

**Additional Comments from Division**

1. *Provide information in the NDA regarding the color of the drug product.*
2. *Please provide detailed information on all manufacturing/testing sites, site address (including street address), contact person (along with telephone and facsimile numbers), and site FIN (formerly CFN). Also, indicate site readiness for inspection.*
3. *It was recommended that an analysis should be done in the ITT population removing all conditions. Everyone receiving at least one dose of product, even if no follow-up was attained, should be included.*

*Also, mention was made of CDISC metadata model document containing examples of analysis datasets put together by the Analysis Dataset Models (ADaM) Working Group. This document was forwarded to the sponsor after the meeting. The sponsor was advised to contact the Project Manger if further discussion of variables to be included in the analysis dataset is needed.*

Minutes created by Lori Gorski, Project Manager

Concurrence Chair: Wiley Chambers, M.D., Deputy Director

*See following page for electronic signatures*

**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  
12/12/02 11:04:26 AM

APPEARS THIS WAY  
ON ORIGINAL



IND 58,997

Nancy S. Yee  
Santen Inc.  
555 Gateway Drive  
Napa, CA 94558

Dear Sponsor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Levofloxacin Hemihydrate Ophthal Sol 15.

We also refer to your amendment dated 4/4/2002, serial number 029, containing information about a new protocol.

The purpose of this letter is to inform you about the Clinical Trials Data Bank available to the public through the Internet at <http://clinicaltrials.gov>. The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Food and Drug Modernization Act of 1997 (Modernization Act).

Section 113 of the Modernization Act amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases, other members of the public, healthcare providers, and researchers. Specifically, the Clinical Trials Data Bank will contain 1) information about clinical trials, both federally and privately funded, of experimental treatments for patients with serious or life-threatening diseases; 2) a description of the purpose of each experimental drug; 3) patient eligibility criteria; 4) the location of clinical trial sites, and 5) a point of contact for those wanting to enroll in the trial. This information must be submitted if the clinical trial concerns a serious or life-threatening disease or condition and if the trial tests effectiveness.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information about clinical trials for serious or life-threatening diseases or conditions to the Clinical Trials Data Bank.

The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system will be made available to the public on the Internet at <http://clinicaltrials.gov>.

Please review the referenced protocol to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, you must submit information about the trial to the Clinical Trials Data Bank, unless you provide detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). You can also submit information about clinical trials under IND that do not meet the criteria described in the Modernization Act.

We appreciate your cooperation. This project is a collaborative effort by the FDA Office of Special Health Issues, the FDA Center for Drug Evaluation and Research (CDER), and NLM/NIH. You will receive a similar letter for each new protocol submitted to a CDER IND during 2002. If you have any questions, contact Theresa Toigo or Janelle Ernat in the Office of Special Health Issues at (301) 827-4460 or e-mail at [113trials@oc.fda.gov](mailto:113trials@oc.fda.gov).

Sincerely,

*{See appended electronic signature page}*

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

Theresa Toigo, RPh, MBA  
Director  
Office of Special Health Issues  
Office of Communications and Constituent Relations  
Office of the Commissioner

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/

-----  
Terry Toigo  
5/24/02 05:55:41 PM

Deborah Henderson  
5/30/02 10:37:03 AM  
for Janet Woodcock, M.D.

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-571	Efficacy Supplement Type SE-	Supplement Number
Drug: Iquix (levofloxacin ophthalmic solution 1.5%)		Applicant: Santen Incorporated
RPM: Lori M. Gorski	HFD-550	Phone # 301-827-2090
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3 – New Formulation
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		March 1, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ 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 type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (i) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Completed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>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!</i>	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
<b>General Information</b>	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(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)	N/A
• Most recent applicant-proposed labeling	February 25, 2004 (package insert)
• Original applicant-proposed labeling	April 30, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS – May 14, 2003 DDMAC – August 8, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	April 30, 2003 (carton & container)
• Reviews	DMETS – May 14, 2003
❖ 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)	In package
❖ Memoranda and Telecons	In package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 27, 2000
• Pre-NDA meeting (indicate date)	November 13, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ 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
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	March 1, 2004 (Medical TL)
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	February 13, 2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	May 15, 2003
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	October 15, 2003
❖ 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)	March 1, 2004
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	December 24, 2003
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	December 24, 2003
❖ 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	December 16, 2003
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	December 2, 2003 February 26, 2003
❖ Environmental Assessment <b>See CMC review</b>	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	September 24, 2003
❖ Facilities inspection (provide EER report)	Date completed: February 24, 2004 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	August 19, 2003
❖ 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

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

/s/

-----  
Lori Gorski  
3/1/04 02:28:31 PM

APPEARS THIS WAY  
ON ORIGINAL

10 Draft Labeling Page(s) Withheld