

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-670

**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**

EXCLUSIVITY SUMMARY FOR NDA # 21-670

Trade Name Vision Blue

Generic Name trypan blue ophthalmic solution

Applicant Name Dutch Ophthalmic Research Center

HFD-550

Approval Date If Known 12-16-04

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

505(b)(1)

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

YES / / NO / ___ /

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

_____ N/A _____

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: N/A

d) Did the applicant request exclusivity?

YES / / NO / /

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

5 Years

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

YES / / NO / /

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

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

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

YES / / NO / /

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES / / NO / /

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

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

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

YES / ___ / NO / X /

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

NDA# _____
NDA# _____
NDA# _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for

any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

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

YES /___/ NO /___/

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

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

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

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

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
!
Investigation #2 !
!
IND # _____ YES /___/ ! 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 /___/

If yes, explain: _____

This document has been prepared by:

Wiley A. Chambers, M.D.
Deputy Division Director

Date *See electronic signature*

Form OGD-011347 Revised 05/10/2004

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/s/

Wiley Chambers
12/16/04 12:22:08 PM

12/16/04

Labeling for NDA 21-670, Trypan Blue

NDA 21-670

Drug: Trypan Blue

Sponsor: Dutch Ophthalmic Research Center, International

Reviewer: Conrad Chen

Date: December 14, 2004

Labeling Sections:

The final recommended labeling is as follows:

Carcinogenesis, mutagenesis, impairment of fertility

Trypan blue was carcinogenic in rats. Wistar/Lewis rats developed lymphomas after receiving subcutaneous injections of 1% trypan blue dosed at 50 mg/kg every other week for 52 weeks (total dose approximately 1,250,000-fold the maximum recommended human dose of 0.06 mg per injection in a 60 kg person, assuming total absorption).

Trypan blue was mutagenic in the Ames test and caused DNA strand breaks in vitro.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Trypan blue is teratogenic in rats, mice, rabbits, hamsters, dogs, guinea pigs, pigs, and chickens. The majority of teratogenicity studies performed involve intravenous, intraperitoneal, or subcutaneous administration in the rat. The teratogenic dose is 50 mg/kg as a single dose or 25 mg/kg/day during embryogenesis in the rat. These doses are approximately 50,000- and 25,000-fold the maximum recommended human dose of 0.06 mg per injection based in a 60 kg person, assuming that the whole dose is completely absorbed.

Characteristic anomalies included neural tube, cardiovascular, vertebral, tail, and eye defects. Trypan blue also caused an increase in post-implantation mortality, and decreased fetal weight. In the monkey, trypan blue caused abortions with single or two daily doses of 50 mg/kg between 20th to 25th days of pregnancy, but no apparent increase in birth defects (approximately 50,000-fold maximum recommended human dose of 0.06 mg per injection, assuming total absorption). There are no adequate and well-controlled studies in pregnant women. Trypan blue should be given to pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Explanation:

In the carcinogenicity section of the labeling, the multiple of animal dose to clinical dose was expressed as 1,250,000-fold because life-time accumulative dose of 50 mg/kg every other week for 52 weeks ($50 \text{ mg/kg} \times 26 = 1300 \text{ mg}$) was used as the basis for calculation. Therefore, the dose ratio was calculated as $1300 \text{ mg} \div 0.001 = 1,300,000\text{-fold}$. This change was made based on the inputs from the medical reviewer. Twenty five doses instead of 26 doses were used by

the medical reviewer in his calculation. Therefore, another calculation showed 1,250,000-fold.

The multiples of animal dose to human dose in the pregnancy section were based on a single dose of 50 mg/kg and 25 mg/kg in animals. Therefore, the ratio in this section was smaller as indicated (50,000- and 25,000-fold).

The human dose, 0.001 mg/kg, was based on 0.06 mg/person in a 60 kg body weight person. Therefore, $0.06 \text{ mg} \div 60 = 0.001 \text{ mg/kg}$ was used as the basis for calculation. The clinical dose of 0.06 mg/injection, instead of 0.18 mg/injection (the maximum dose), was used in the calculation per medical reviewer's recommendation.

Conrad H. Chen, Ph.D.
Pharmacology Reviewer

Concurrence by: Josie Yang, Ph.D.
Pharmacology Team Leader

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/s/

Conrad Chen
12/16/04 04:04:17 PM
PHARMACOLOGIST

Josie Yang
12/16/04 05:04:59 PM
PHARMACOLOGIST
The human equivalent dose multiples shown in the carcinogenicity
section of the labeling were derived from life-time
accumulative dose of 50 mg/kg every other week
for 52 weeks in rats. This calculation method
is not a common practice with the center.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-670 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: October 27, 2003 Action Date: April 27, 2004

HFD 550 Trade and generic names/dosage form: Vision Blue (trypan blue) Intraocular Injection, 0.06%

Applicant: D.O.R.C., International Therapeutic Class: Diagnostic Agent: Dye

Indication(s) previously approved:

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

Number of indications for this application(s): one

Indication #1: _____

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 range being deferred:

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. 3 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 15 Tanner Stage _____

Comments: The use of Trypan Blue in pediatric patients is supported by adequate and well controlled studies.

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:

{See appended electronic signature page}

Nancy Halonen
Regulatory Project Manager

cc: NDA 21-670
HFD-960/ Grace Carmouze

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/s/

Nancy Halonen
4/27/04 11:11:46 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-670	Efficacy Supplement Type SE-	Supplement Number
Drug: VisionBlue (trypan blue ophthalmic solution), 0.06%		Applicant: DORC International, B.V.
RPM: Lori Gorski		HFD-550 Phone # 301-827-2521
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority NME N/A
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		December 16, 2004 <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		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		<input type="checkbox"/> Paid UF ID number NONE <input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

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

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

Yes No

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

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

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

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	NME - summary 12/16/04
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM - 4/12/04, 4/27/04

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE – April 27, 2004
• 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	() None () Press Release (X) 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	December 6, 2004
• Original applicant-proposed labeling	October 24, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC – 11/25/03 & 3/18/04 DMETS – 4/2/04 & 9/13/04
• 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	December 6, 2004
• Reviews	See MO review of 12/13/04
❖ 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)	See package
❖ Memoranda and Telecons	See package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	November 29, 2004
• 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

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Clinical Team Leader – 4/26/04, 12/15/04 ODEV – 4/26/04, 12/16/04
❖ Clinical review(s) <i>(indicate date for each review)</i>	4/12/04, 12/13/04
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	MO review of 12/13/04
❖ 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)	4/27/04
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	4/1/04
❖ 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	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	4/16/04, 12/1/04, 12/13/04, 12/15/04
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	See CMC review
• Review & FONSI <i>(indicate date of review)</i>	See CMC review
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	See CMC review
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	4/5/04, 8/24/04, 10/1/04
❖ Facilities inspection (provide EER report)	Date completed: See CMC review (X) Acceptable 12/15/04 () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	3/5/04, 5/12/04, 11/12/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

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/s/

Lori Gorski
12/16/04 12:17:21 PM

Office Director Memorandum
NDA 21-670

Date: December 15, 2004
Proposed Tradename: VisionBlue
Drug Name: Trypan blue intraocular solution 0.06%
Pharmacologic Class: Ocular tissue staining agent

Applicant: DORC International B.V.
Previous Action Letter: April 17, 2004
PDUFA Goal Date: December 16, 2004

Dosage form and Route of administration: intracameral administration of 0.1 to 0.3mL after filling the anterior chamber with air

Proposed Indication: —

This memorandum provides for Office concurrence with the Division recommendation for an approval action for this response to the action letter of April 11, 2004. The applicant has provided data which adequately address the outstanding regulatory concerns to assure product manufacturing integrity for this product and its proposed indication and setting of use.

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/s/

Jonca Bull
12/16/04 10:00:17 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: December 13, 2004

FROM: William Boyd, M.D.
Clinical Team Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

TO: Brian Harvey, M.D., Ph.D.
Acting Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

SUBJECT: NDA 21-670 Vision Blue (trypan blue intraocular solution) 0.06%

I concur with the analyses and conclusions reached in the Medical Officer's second Clinical Review, signed off in the electronic Document File System (DFS) on December 13, 2004, for NDA 21-670 Vision Blue (trypan blue intraocular solution) 0.06%.

NDA 21-670 is recommended for approval from a clinical prospective with the labeling identified in this second review.

cc:
NDA 21-670
HFD-105/Office Dir/Bull
HFD-105/ADRA/Rumble
HFD-550/Sup CSO/DeBellas
HFD-550/Div Dir/Harvey
HFD-550/MO/Chambers
HFD-550/CSO/Gorski

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/s/

William Boyd
12/14/04 09:18:38 AM
MEDICAL OFFICER

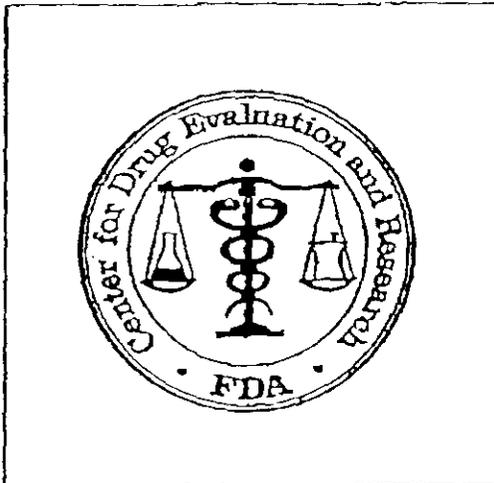
Brian Harvey
12/15/04 09:41:39 AM
MEDICAL OFFICER

*** TX REPORT ***

TRANSMISSION OK

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CONNECTION TEL		916036428465
CONNECTION ID	DUTCH OPHTHALMIC	
ST. TIME	12/10 16:18	
USAGE T	00'42	
PGS. SENT	2	
RESULT	OK	

FACSIMILE TRANSMISSION
RECORD



From: Yongde Lu, Ph.D.

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

Phone 301 827-2040

Fax 301-827-2531

Date: 12/10/04

To: Name Fran Carleton
 Company Dutch Ophthalmics USA
 Address _____
 City Kingston State NH 03848
 Phone (603) -642-8468
 FAX # (603)-642-8465
 Number of Pages (INCLUDING COVER PAGE) 2

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

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If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified

ysical
on

December 10, 2004

NDA 21-670

Vision Blue

Based on the information for — data, Interim Stability Report FE01/04 rev.3 dated 12/8/04 via e-mail and the HPLC chromatograms dated 11/29/04 via the facsimile. The following revised specification for VisionBlue® 0.06% is recommended:

Specification of VisionBlue® (Trypan Blue Ophthalmic Solution, 0.06%)

TEST	ACCEPTANCE CRITERIA	METHOD (CODE #)
Physical Appearance	/	Vision inspection
Trypan Blue Identity	/	/
Trypan Blue Assay	/	/
Trypan Blue Assay (Stability study)	/	HPLC /
Impurities:		HPLC: /
/	/	
/	/	
Any individual unspecified impurity	NMT /	
Total impurities	NMT /	
pH	7.3 – 7.6	/ according to USP<791>
Osmolality	257 – 314 mOsm / kg	/ according to USP<785>
Particulate Matter	NMT / NMT / NMT /	USP<789>
Sterility	sterile	/

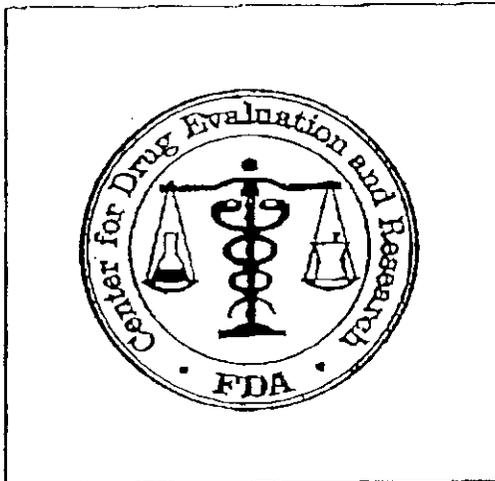
3 Draft Labeling Page(s) Withheld

*** TX REPORT ***

TRANSMISSION OK

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CONNECTION ID	DUTCH OPHTHALMIC	
ST. TIME	12/06 17:51	
USAGE T	00'41	
PGS. SENT	2	
RESULT	OK	

FACSIMILE TRANSMISSION
RECORD



From: Yongde Lu, Ph.D.

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

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

Date: 12/6/04

To: Name Fran Carleton
 Company Dutch Ophthalmic USA
 Address _____
 City Kingston State NH 03848
 Phone (603) 642-8468
 FAX # (603) 642-8465
 Number of Pages (INCLUDING COVER PAGE) 2

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

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December 6, 2004

NDA 21-670

Vision Blue

The specification for VisionBlue® 0.06% is recommended based on _____ wavelength of the UV detector from _____ chromatogram.

Specification of VisionBlue® 0.06% Trypan Blue Ophthalmic Solution

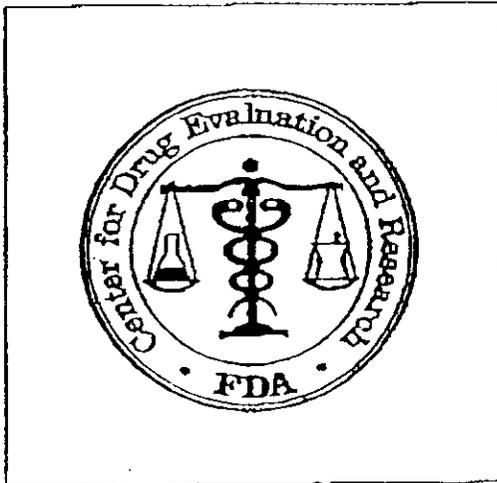
TEST	ACCEPTANCE CRITERIA	METHOD (CODE #)
Physical Appearance		Vision inspection
Trypan Blue Identity	/	/
Trypan Blue Assay	/	/
Impurities:		HPLC
Unspecified impurities	NMT /	
Total impurities	NMT	
pH	7.3 - 7.6	
Osmolality	257 - 314 mOsm / Kg	/ according to USP<791> according to USP<785>
Particulate Matter	NMT : NMT / NMT	USP<789>
Sterility	sterile	/

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO	2367	
CONNECTION TEL		916036428465
CONNECTION ID	DUTCH OPHTHALMIC	
ST. TIME	11/30 10:24	
USAGE T	00:47	
PGS. SENT	2	
RESULT	OK	

FACSIMILE TRANSMISSION
RECORD



From: Yongde Lu, Ph.D.

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

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

Date: 11/30/04

To: Name Fran Carleton
Company Dutch Ophthalmic USA
Address _____
City Kingston State NH 03848
Phone (603) 642-8468
FAX # (603) 642-8465
Number of Pages (INCLUDING COVER PAGE) 2

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November 30, 2004

NDA 21-670

Vision Blue

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. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per 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.

1. In order to support the finalized drug product specification, please submit the release data for at least _____ of drug product made from the _____ trypan blue using the finalized drug product specification. Alternatively, submit testing results of samples from the on-going stability studies of the drug product made from _____ trypan blue using the finalized drug product specification.
2. Based on the finalized specification of the drug product, please update Section 3.6 "Test parameters, methods, and Specifications (Acceptance Criteria) of the stability protocol" located in Attachment 7 of Amendment dated 6/11/2004.

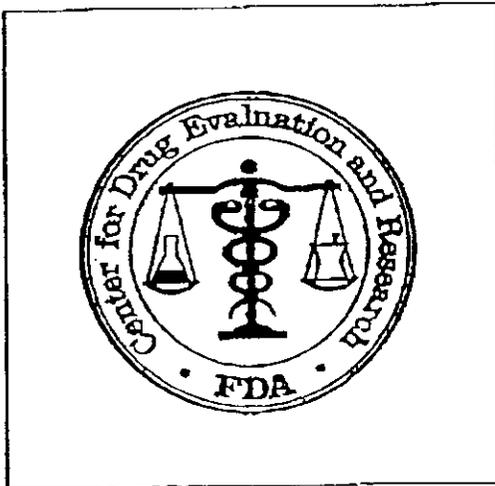
*Appears This Way
On Original*

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO	2272	
CONNECTION TEL		916036428465
CONNECTION ID	DUTCH OPHTHALMIC	
ST. TIME	10/29 17:33	
USAGE T	01'00	
PGS. SENT	3	
RESULT	OK	

FACSIMILE TRANSMISSION
RECORD



From: Yongde Lu, Ph.D

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

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

Date: 10/29/04

To: Name Fran Carleton
 Company Dutch Ophthalmic USA
 Address _____
 City Kingston State NH
 Phone (603) 642-84868
 FAX # (603) 642-8465

Number of Pages (INCLUDING COVER PAGE) 3

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

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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 301-827-2040.

October 29, 2004
~~August 29, 2004~~

NDA 21-670

Vision Blue

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. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per 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.

1. Please address following issues for the specification of VisionBlue@0.06% submitted in 10/14/04 amendment.
 - Trypan Blue assay should be performed by HPLC or plus HPLC, because only is not stability indicating for stability studies.
 - Impurities assay should be listed as the Format below:

Retention time ???	NMT X %
Retention time ???	NMT Y %
-----	-----
Any individual unspecified	NMT <input type="checkbox"/>
Total Impurities	NMT W %
 - Submit a representative chromatogram of HPLC for VisonBlue@0.06% using the drug substance made by
 - Submit the chemical structure of impurity

2. Based on the commitment dated 10/11/04 please provide the stability data on VisionBlue@0.06% filled in glass syringes and closed with stopper as early as the data become available.

3. Provide study data for the 2.25 ml syringe system using HPLC method with lower detection UV wavelength, when filled with the drug product. Following is a proposed testing procedure:

APPEARS THIS WAY
ON ORIGINAL

MEMO

To: Brian Harvey, MD, PhD
Acting Director, Division of Analgesics, Anti-Inflammatory and Ophthalmic Drug Products
HFD-550

From: Kristina C. Arnwine, PharmD.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Denise P. Toyer, Pharm.D.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Nancy M Halonen
Project Manager, Division of Analgesics, Anti-Inflammatory and Ophthalmic Drug Products
HFD-550

Date: September 10, 2004

Re: ODS Consult 03-0298-2, Vision Blue (Trypan Blue) 0.06%; NDA 21-670

This memorandum is in response to a June 11, 2004 request from your Division for a final review of the proprietary name, Vision Blue. The revised container label and insert labeling were not provided for review and comment. Please refer to ODS Consult 03-0298-1 for DMETS' recommendations regarding labels and labeling for Vision Blue.

DMETS has not identified any additional proprietary names as having potential sound-alike and look-alike confusion with Vision Blue since we conducted our initial and follow-up reviews dated February 4, 2004 and April 2, 2004 that would render the name objectionable (see ODS Consults 03-0298 and 03-0298-1). DDMAC found the proprietary name, Vision Blue, unacceptable from a promotional perspective. DDMAC stated that the

In summary, DMETS has no objection to the use of the proprietary name, Vision Blue from a safety perspective. However, DDMAC objects to the name from a promotional perspective. Please contact DDMAC reviewer Debi Tran to discuss further. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and

labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Kristina Arnwine
9/13/04 03:19:17 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/13/04 03:49:14 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/04 03:56:23 PM
DRUG SAFETY OFFICE REVIEWER

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: Fran Carlton, DORC

From: Lori Gorski, Project Manager

Fax: 603-642-8465

Fax: 301-827-2531

Phone: 603-642-8468

Phone: 301-827-2521

Pages: 1 (including cover page)

Date: September 3, 2004

Re: NDA 21-670 reviewer requests and deficiencies

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

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• **Comments:**

Hi Fran,

After review of the submission dated June 11, 2004, the following microbiology items have been identified as deficiencies by the reviewers for the _____ application. Please respond with an amendment(s) to NDA 21-670 to provide the following information to the application:

1. A detailed description of the materials, methods and results of the (_____) test used to demonstrate container integrity. Provide acceptance criteria for the test, descriptions of the positive and negative controls, and the number of units tested.
2. A detailed description of the materials, methods, and results of _____ testing. Provide the results of _____ testing at the _____

Please include a form FDA-356h with every submission. Let me know if you have any questions.

Thanks,
Lori Gorski

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ON ORIGINAL

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

/s/

Lori Gorski
9/3/04 02:44:18 PM
CSO

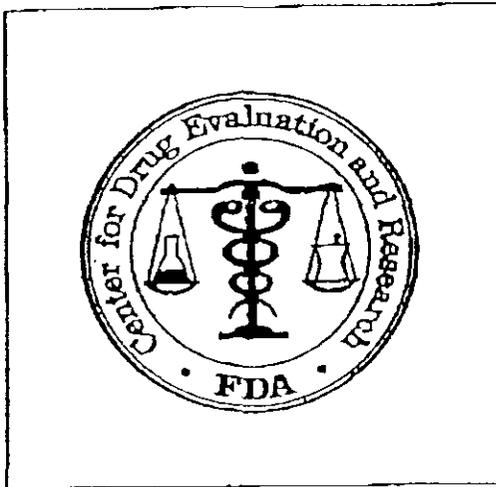
Lori Gorski
9/3/04 02:50:26 PM
CSO
faxed to sponsor 9/3

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO 2058
CONNECTION TEL 916036428465
CONNECTION ID DUTCH OPHTHALMIC
ST. TIME 08/02 10:36
USAGE T 01'00
PGS. SENT 3
RESULT OK

FACSIMILE TRANSMISSION
RECORD



From: Yongde Lu, Ph.D.

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

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

Date: 8/2/04

To: Name Fran Carleton
Company Dutch Ophthalmic USA
Address _____
City Kingston State NH
Phone (603) 642-8468

FAX # (603) 642-8465

Number of Pages (INCLUDING COVER PAGE) 3

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August 2, 2004

NDA 21-670

Vision Blue

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. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per 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.

1. Please submit a tabulated specification of the drug product, VisionBlue™ as shown below, including a list of tests, reference analytical methods, and acceptance criteria.

Specification for Vision Blur® Ophthalmic Solution, 0.06%

TEST	ACCEPTANCE CRITERIA	METHOD (CODE #)
Physical Appearance		
Trypan Blue Identity		UV and HPLC
Trypan Blue Assay	??.?? to ???.??% of Label	HPLC
Impurities: Specified (by name or retention time) impurities Any individual unspecified impurities Total impurities	NMT ?.??% of trypan blue Label NMT — , of trypan blue Label NMT ?.??% of trypan blue Label	HPLC
pH	?? - ??	USP<791>
Osmolality	??? - ??? mOsm / Kg	USP<785>
Particulate Matter	NMT NMT NMT	

Sterility		/
-----------	--	---

2. Please provide a sample of the whole packaging system of the _____ including the peel pouch for evaluation.
3. Submit the LOA with a reference to the DMF for _____, and _____ . Include the page number and submission date.
4. Submit _____) study data for the syringe system using the HPLC method with a lower detection wavelength, when filled with both drug product and water.
5. Based on the revised specification of the drug product, and the ICH Q1A(R2) Guidance, please submit at least _____ accelerated stability data and _____ long term stability data in a table form for _____ batches of the drug product packed in the proposed syringe. In addition,, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for _____ .
6. Please follow the ICHQ1A(R2)Guidance for the following testing frequency in the stability studies of the drug product.

Long-term studies	_____	months
Accelerated studies	_____	months

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-670

D.O.R.C. International B.V.
Attention: Fran Carleton
Operations Manager
One Little River Road
P.O.Box 968
Kingston, NH 03848

Dear Ms. Carleton:

Please refer to your Supplemental New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vision Blue (trypan blue injection) 0.06%.

We also refer to the teleconference meeting between representatives of your firm and the FDA on July 16, 2004. The purpose of the meeting was to discuss chemistry and manufacturing issues for the pending application.

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

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

Sincerely,

{See appended electronic signature page}

Linda L. Ng, Ph.D.
Chemistry Team Leader for the
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure

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

DATE: July 16, 2004

BETWEEN: Representing: D.O.R.C International, B.V.

Frank Ruseler, VP, DORC Int'l
JanKees Wouts, Product Engineer
- Consultant,
- Consultant, DORC Int'l
Ger Vijfvinkel
Fran Carleton, Operations Manager, Dutch Ophthalmic, USA

AND Representing: _____

/
/

AND FDA

Wiley Chambers, M.D., Deputy Division Director
Linda Ng, Ph.D., Team Leader, CMC
Yong de Lu, Ph.D., CMC Reviewer
Nancy Halonen, Project Manager
Carmen DeBellas, Chief, Project Manager
Lori Gorski, Project Manager

SUBJECT: NDA 21-670 CMC issues.

BACKGROUND: NDA 21-670 was submitted as a 505(b)(2) application. An approvable letter was issued on April 27, 2004. The Applicant requested this teleconference to discuss GMP compliant drug substance and their alliance with _____ working towards a DMF.

DISCUSSION:

- DORC informed the Agency that _____ nas agreed to produce cGMP complaint trypan blue.
- DORC queried where _____ needed to start the cGMP manufacturing process and the Agency clarified that the process may start with purification under cGMP conditions with the trypan blue synthesized within _____
- _____ explained that they were successfully inspected by the FDA in 2002 at their _____, site, and will be ready for an inspection. _____ was told that an inspection of their site will be requested.

- [redacted] stated that they planned to file a Type 2 DMF at their [redacted] site. The Agency advised [redacted] to incorporate a flow chart, a description of the trypan blue synthesis, [redacted] process with validation, and [redacted] accelerated and room temperature stability data in the DMF. It is acceptable to submit the DMF early, and amended the DMF with updated stability data.

AGREEMENTS:

[redacted] will [redacted] trypan blue under cGMP conditions and will submit a type II DMF for trypan blue to contain the synthesis [redacted] and stability of the drug substance.

DORC will commit to put batches of the drug product made from the [redacted] drug substance on stability.

Minutes prepare: Nancy Halonen, Project Manager

Concurred: Linda Ng, Ph.D, Chemistry Team Leader
See appended signature page

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/s/

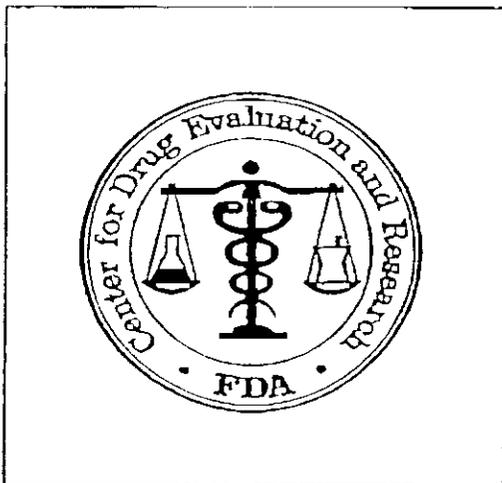
Linda Ng
7/28/04 09:09:12 AM

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO	2040	
CONNECTION TEL		916036428465
CONNECTION ID	DUTCH OPHTHALMIC	
ST. TIME	07/26 10:39	
USAGE T	00'44	
PGS. SENT	2	
RESULT	OK	

FACSIMILE TRANSMISSION
RECORD



From: Yong de Lu

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

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

Date: 7/26/04

To: Name Fran Carleton
 Company Dutch Ophthalmic USA
 City Kingston State NH
 Phone # (603) 642-8468

FAX # (603) 642-8465

Number of Pages (INCLUDING COVER PAGE) 2

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July 26, 2004

NDA 21-670

Vision Blue

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. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per 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.

In order to conduct the cGMP inspection of the manufacturing site for the drug substance, trypan blue, please provide the following information:

- a. full name of the firm and establishment registration number or CFN if available
- b. detail street address of the manufacturing site
- c. name of the contact person
- d. telephone number and fax number

**APPEARS THIS WAY
ON ORIGINAL**

4/27/04

Updated NDA REGULATORY FILING REVIEW

NDA # 21-670
Trade Name: Vision Blue
Generic Name: trypan blue
Strengths: 0.06%

Applicant: Dutch Ophthalmic Research Center, International
Date of Application: October 24, 2003
Date of Receipt: October 27, 2003
Date clock started after UN: N/A
Date of Filing Meeting: November 25, 2003
Filing Date: December 26, 2003
Action Goal Date : March 24, 2004

Indication requested: to provide contrast to aid in visualization of the anterior lens capsule when performing the capsulorhexis in cataract surgery.

Type of Original NDA: (b)(1) _____ (b)(2) **X** _____
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: **Priority Application**

Resubmission after withdrawal? NO Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 1

Other (orphan, OTC, etc.) _____

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

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

User Fee ID # N/A (waived)

Clinical data? **NO X No NDAs referenced, multiple European peer reviewed articles referencing previous clinical studies, most in English, some in German and French.**

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO

- **Originally, signed by Foreign Signatory only. (If foreign applicant, both the applicant and the U.S. Agent must sign the certification.) US agent and Applicant co-signed the Debarment certificate.**

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
 "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? **YES** **NO**
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

The Applicant claims these forms are not relevant since the NDA is supported by peer-reviewed articles referencing previous clinical studies authored by clinicians not invested in the NDA product. Financial Information has not been submitted. Sponsor was notified on April 16, 2004, that they must submit FDA Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators and FDA Form 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators.

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** **NO**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** **NO**
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **None Listed**

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

- Pre-NDA Meeting(s)? **Date(s) _____** **NO**
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES** **NO**

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES** **NO**

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A** **YES** **NO**

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **N/A** **YES** **NO**

If Rx-to-OTC Switch application:

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

X 21 CFR 314.50(i)(1)(i)(A)(4): **The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.**

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

N/A

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

N/A IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

ACTION ITEMS:

Outstanding regulatory issues have been conveyed to the Sponsor to be addressed in the next review cycle.

Nancy M. Halonen
Regulatory Project Manager

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/s/

Nancy Halonen
4/27/04 11:20:42 AM
CSO

Office Director Memorandum

Date: April 26, 2004

Re: NDA 21-670

Submission Date: October 27, 2003

Drug Product: Trypan Blue Ophthalmic Solution 0.06%

Proposed Trade Name: Vision Blue

Sponsor: Dutch Ophthalmic Research Center

Proposed indication/use: —

Background

Trypan blue is a vital stain with a long history of use in dye exclusion procedures for viable cell counting based on the principle that live cells do not take up certain dyes. The proposed product is intended for use in the setting of cataract surgery to facilitate visualization of the anterior capsular lens. There is also an extensive history of use in support of corneal transplant surgery.

Vision Blue has been approved in Europe as a Class IIa medical device since 1999. The applicant reports that over — units have been used in the setting of cataract surgery.

It is noted that the proposed product has been the subject of a "Request for Jurisdiction" dated May 16, 2000, requesting classification of Trypan Blue as a device. FDA concluded that Trypan Blue should be regulated as a drug due to the differential staining property associated with its use. The applicant subsequently submitted a "Request for Reconsideration" to the Office of the Ombudsman on May 3, 2002 asserting that the product is consistent with the definition of a device and would impose a significant and unfair competitive disadvantage on Dutch Ophthalmics with no scientific basis. The agency again concluded that the proposed product meets the definition of a drug as an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man; and /or an article intended to affect the structure or any function of the body.

Clinical

The submitted NDA does not include well controlled clinical trials conducted by the sponsor specific to the proposed indication. Instead, the sponsor has submitted medical literature consisting of reports of usage in the setting of cataract surgery as well as recent studies in the setting of retinal surgery. The studies cited in the table of the clinical review provide data on a total of approximately 400 patients, overwhelmingly for cataract surgery. There is one study cited in the review which evaluated use in pediatric patients.

The only safety issue noted is that of unanticipated staining of a hydrogel lens.

Chemistry and Manufacturing

There are significant CMC deficiencies which are discussed in detail in Dr. Lu's review. Of particular concern is the lack of CMC information for the drug substance, no DMF on file, and a lack of clarity as to the actual manufacturer of trypan blue and provision of a site for inspection by the Agency.

Labeling Comments

The labeling should provide a brief summary of the clinical data reviewed from the literature on which the finding of clinical efficacy and safety is based.

The draft label in the action package states that adequate and well controlled trials have been conducted in pediatric patients. This implies a much higher standard of trial than the data submitted appears to represent. I am unable to substantiate well controlled trials in the clinical review. It is recommended that this section of the label revisit the sufficiency of the data submitted as "well controlled" and its adequacy for recommendation of use of the product in pediatric patients.

Consideration should be given to more specificity on dosing than that of

Conclusions

Given the scope of outstanding CMC issues, an approvable action is appropriate. Although there is a paucity of controlled clinical trial data in this application, there appears to be sufficient literature and experience with the product to support its proposed use for safety and efficacy.

The sponsor should be advised of the need to provide safety updates on any new clinical data.

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On Original*

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/s/

Jonca Bull
4/27/04 10:53:59 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: April 26, 2004

FROM: William Boyd, M.D.
Clinical Team Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

TO: Brian Harvey, M.D., Ph.D.
Acting Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

SUBJECT: NDA 21-670 Vision Blue (trypan blue intraocular solution) 0.06%

I concur with the analyses and conclusions reached in the Medical Officer's Clinical Review, signed off in the electronic Document File System (DFS) on April 12, 2004, for NDA 21-670 Vision Blue (trypan blue intraocular solution) 0.06%.

NDA 21-670 is recommended for approval from a clinical prospective with the labeling identified in this review.

cc:
NDA 21-670
HFD-105/Office Dir/Bull
HFD-105/ADRA/Rumble
HFD-550/Sup CSO/DeBellas
HFD-550/Div Dir/Harvey
HFD-550/MO/Chambers
HFD-550/CSO/Halonen

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/s/

William Boyd
4/26/04 01:00:30 PM
MEDICAL OFFICER

Brian Harvey
4/26/04 02:03:44 PM
MEDICAL OFFICER

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: Fran Carleton **From:** Nancy Halonen
Fax: (603) 642-8468 **Fax:** 301-827-2531
Phone: (603) 642-8465 **Phone:** 301-827-2199
Pages: (3 including cover page) **Date:** April 19, 2004
Re: Meeting Minutes for CMC teleconference April 9, 2004 for NDA 21-670 (Vision Blue).

Urgent For Review Please Comment Please Reply Please Recycle

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• **Comments:**

Good afternoon Fran,

Enclosed please find the teleconference minutes for April 9, 2004 held between DORC representatives and the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products for NDA 21-670 (Vision Blue).

I hope these prove helpful to you.
Sincere regards,
Nancy Halonen

April 19, 2004

DATE: April 9, 2004

APPLICATION NUMBER: NDA 21-670, Vision Blue (trypan blue) Intraocular Injection, 0.06%

BETWEEN:

Name:

Frank Ruseler, VP DORC Int'l
JanKees Wouts, Product Engineer
—, Consultant
—, Consultant, DORC Int'l
Fran Carleton, Operations Manager, Dutch Ophthalmic, USA

Representing: D.O.R.C International. B.V.

AND

Name: Nancy Halonen, Project Manager
Linda Ng, Ph.D., Team Leader, CMC
Yong de Lu, Ph.D., CMC Reviewer

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

SUBJECT: To discuss issues in the NDA.

BACKGROUND: The Applicant requested this teleconference to inform the Agency of progress working with — to reveal the original manufacturer of trypan blue drug substance, status of the CMC issues that need to be addressed, and to learn if the Agency has had any dialogue with — about the original manufacturer of trypan blue.

DISCUSSION:

The Applicant has attempted to find alternative sources of trypan blue but has been unsuccessful. The Applicant informed the Agency that — had been contacted and was agreeable to disclose the identity of the original manufacturer of trypan blue. The Agency informed the Applicant that — has agreed to reveal the original manufacturer of trypan blue's identity and that positive discussion is ongoing between — and the Agency.

The Applicant has just submitted a CMC amendment that they feel answers all but 2 of our outstanding CMC issues. The Applicant continues to do analytical testing and will submit more information after further investigation.

The Applicant stated they were preparing for the Agency site inspection of — next week.

The Applicant informed the Agency, when asked, that Vision Blue has been approved in Europe and Canada as a medical device, and has been marketed for 4 years in Europe.

April 19, 2004

The Agency urged the Applicant to continue submitting CMC information as it becomes available.

DECISIONS AND AGREEMENTS:

The Applicant will submit all the analytical data as it becomes available to the Agency.

The Agency and the Applicant will maintain ongoing dialogue as needed regarding issues in the NDA application.



Linda Ng, Ph.D.
Team Leader, CMC

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/s/

Nancy Halonen
4/19/04 12:48:07 PM
CSO

Linda Ng
4/19/04 01:03:23 PM
CHEMIST

e-mail information request sent to DORC on April 16, 2004.

Good morning Fran,

The Agency will need you to submit financial disclosure information from DORC. **You will need to fill out all three of the forms below and submit them to the application.** Two are financial information forms and one is the FDA Form 3542a: *Patent Information Submitted with the Filing of an NDA, Amendment or Supplement* which must be completed and submitted, as discussed in early March.

FDA Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators

<http://forms.psc.gov/forms/FDA/FDA-3454.pdf>

FDA Form 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators

<http://forms.psc.gov/forms/FDA/FDA-3455.pdf>

FDA Form 3542a Certification: Patent Information Submitted with the Filing of an NDA, Amendment or Supplement

<http://forms.psc.gov/forms/FDA> and scroll down to FDA 3542a.pdf

We need this information as soon as possible. Please let me know when you think they can be submitted.

Thank you,

Nancy

CDR Nancy M. Halonen
Regulatory Health Project Manager
FDA/CDER/ODE V

Room N343
Office: 301-827-2199
Fax: 301-827-2531
Email: halonenn@cder.fda.gov

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/s/

Nancy Halonen
4/16/04 06:15:21 AM
CSO

MEMO

To: Brian Harvey, M.D., Ph.D.
Acting Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products HFD-550

From: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Carol A. Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety, HFD-400

CC: Nancy M. Halonen
Project Manager, Division of Anti-Inflammatory, Analgesic and ophthalmologic Drug Products HFD-550

Date: March 30, 2004

Re: ODS Consult 03-0298-1, Vision Blue (Trypan Blue) 0.06%; NDA 21-670

This memorandum is in response to a March 5, 2004 request from your Division for a review of the container labels, carton and insert labeling for Vision Blue.

The proposed proprietary name, Vision Blue was found acceptable by DMETS on February 4, 2004 (ODS Consult 03-0298). DDMAC found the proprietary name, Vision Blue. unacceptable from a promotional perspective.

In the review of the Vision Blue container labels, carton and insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. General Comments

1. The container labels and carton labeling
2. Revise the labels and labeling so that the established name, strength, and the dosage form appear in conjunction with the proprietary name. For example:

Vision Blue
(Trypan Blue Injection) 0.06%

3. Revise the container label and the carton labeling to include the route of administration and a usual dose statement.
4. Revise the abbreviation of milliliters from 'ml.' to read 'mL'

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/s/

Denise Toyer
4/2/04 02:37:13 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/2/04 03:13:15 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: March 19, 2004

APPLICATION NUMBER: NDA 21-670, Vision Blue (trypan blue) Intraocular Injection, 0.06%

BETWEEN:

Name:

Frank Ruseler, VP DORC Int'l
JanKees Wouts, Product Engineer
 ~ Consultant
 - Consultant
Fran Carleton, Operations Manager, Dutch Ophthalmic, USA

Representing: D.O.R.C International. B.V.

AND

Name: Nancy Halonen, Project Manager
Linda Ng, Ph.D., Team Leader. CMC
Yong de Lu, Ph.D., CMC Reviewer

Representing:

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

SUBJECT: The Agency requested this teleconference to discuss outstanding CMC issues.

1. The Applicant raised concerns about how to proceed with submitting CMC information since they are having difficulty gaining cooperation from ~ to divulge the identity of the manufacturer of the drug substance.
2. The Agency recommended that the Applicant make one more attempt to convince ~ to supply the necessary drug substance manufacturing information directly to the FDA, assuring ~ that the Applicant will not be apprised to any of the information.
3. The Applicant was asked to think about alternative plans for obtaining the needed CMC information if ~ ultimately refuses to divulge/yield their information to the FDA. The Applicant stated they would explore other suppliers for trypan blue.
4. The Applicant currently has been doing analytical testing of the drug substance themselves, but has not completed the testing yet. The Applicant states they have found ~ impurity. The Agency would like to have a mass balance in the drug substance. The Applicant was encouraged to send to the Agency the results of the analytical testing before the next scheduled teleconference.
5. The Applicant stated the planned switch from ~ to syringe will occur on April 4, 2004.

Decisions and Agreements:

The Applicant will contact _____ one more time about submitting the drug substance information or filing a DMF directly to the FDA.

The Applicant will submit all the analytical data they have available about the drug substance to the Agency.

The Applicant will ascertain from _____ the time frame for submission of chemistry and manufacturing information for the drug substance to the Agency.

The Agency will internally discuss possibilities of working on the drug substance source issues.

Linda Ng, Ph.D.
Team Leader, CMC

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/s/

Nancy Halonen
4/5/04 10:11:33 AM
CSO

Linda Ng
4/5/04 11:33:14 AM
CHEMIST

5 **Pages Redacted of
Deliberative Process
§ 552(b)(5)**

E-mail Information request to sponsor on 3-17-04

Good morning again Fran,

Our label review team is requesting a color version of the labels and labeling to be supplied to us.
Would you be able to get those for me?

Thanks again,

Nancy

CDR Nancy M. Halonen
Regulatory Health Project Manager
FDA/CDER/ODE V

Room N343

Office: 301-827-2199

Fax: 301-827-2531

Email: halonenn@cder.fda.gov

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/s/

Nancy Halonen
3/17/04 06:23:29 AM
CSO

E-mail information request 3-5-04

Good morning Fran.

I just spoke with [redacted] regarding some delays with CMC information coming from Europe. Frank also wanted clarification on exclusivity rights. Trypan Blue is a New Molecular Entity, so your company may request 5 years of exclusivity. My division does not determine the exclusivity rights. This happens with an exclusivity board. You also hold all the clinical information for trypan blue, so I don't suspect anyone else will be applying for an NDA in the near future.

DORC also owns the patent for trypan blue. Patent exclusivity is different from other kinds of exclusivity and can only be determined by patent lawyers.

I will need you to fill out a form 3542a, Patent Information, and send it as an amendment to the NDA. I neglected to tell you that I needed this form as I reviewed the NDA for regulatory content. Here is a link to all FDA forms that you might need.

<http://forms.psc.gov/forms/FDA/fda.html>

I wish you a wonderful weekend!

Regards,

Nancy

CDR Nancy M. Halonen
Regulatory Health Project Manager
FDA/CDER/ODE V

Room N343
Office: 301-827-2199
Fax: 301-827-2531
Email: halonenn@cder.fda.gov

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/s/

Nancy Halonen
3/17/04 06:21:22 AM
CSO

MEMORANDUM OF TELECON

DATE: February 13 2004

APPLICATION NUMBER: NDA 21-670, Vision Blue (trypan blue) Intraocular Injection, 0.06%

BETWEEN:

Name:

Frank Ruscler, VP DORC Int'l
JanKees Wouts, Product Engineer
— MD, PhD, Corneal Surgeon, Consultant
— Consultant
Fran Carleton, Operations Manager, Dutch Ophthalmic, USA

Representing: D.O.R.C International B.V.

AND

Name: Nancy Halonen, Project Manager
Linda Ng, Ph.D., Team Leader, CMC
Yong de Lu, Ph.D., CMC Reviewer

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

SUBJECT: The Applicant requested this teleconference to discuss CMC issues. The following advice was given to the Applicant:

1. The Applicant raised concerns about whether trypan blue is the active ingredient or the starting material for Vision Blue. The Applicant stated that the trypan blue is a staining agent, and argued it is a non-metabolic drug. The Agency clarified that the definition of a drug substance is that the substance is doing the job that is being claimed, which in this case is staining. Thus, trypan blue is the active drug component, and not a starting material.
2. The Applicant stated that — is the manufacturer — of trypan blue. The Agency reiterated that the Applicant would need to get the specific detailed manufacturing process information from —. The Agency commented that this requirement for detailed manufacturing process information is the standard for all drug substance review in the Agency, and that the Division cannot rely on literature.
3. The Applicant stated that trypan blue is not manufactured as a drug substance for pharmaceutical use —, and D.O.R.C. does not know if a DMF is available or whether the manufacturing site is practicing with GMP standards. All drug substances and drug product manufacturing and testing (release and stability) sites normally have to pass inspection before approval of an NDA. The drug product manufacturing includes packaging and labeling. The Agency recommends that the Applicant finds out from — if they will provide the synthesis process, the controls and relevant data or be willing to submit a DMF for trypan blue.

4. The NDA needs data to support that the Applicant has a good understanding and control of the manufacturing process to ensure that the drug substance is reproducible today, tomorrow, and in the future. This also applies to the drug product.
5. The Agency agreed it would be beneficial to provide chromatographic analysis testing for purity profiling. Tracking and limiting the impurities, e.g., the _____ impurity would be helpful towards understanding the product.
6. The Applicant clarified that they have changed the marketing packaging from _____ to a syringe because the syringe is the way the drug product is currently marketed in Europe.
7. The submission should be an amendment to the NDA, not a revision of the NDA, but a complete separate response to each question that is asked. Each amendment that is submitted to the Agency should be accompanied by a form 356h, and be dated, and the section that states "type of submission" should be checked in the appropriate box: amendment to a pending application, or any of the other selections that may apply. The submissions will be coded and tracked in our document room to help the Applicant and Agency for references in discussions of issues identified.
8. Each question that the Agency identifies with a number should be addressed with a separate definitive response. There should be no pooling of answers in a group.

Decisions and Agreements:

The Applicant will contact _____ about submitting the drug substance information or filing a DMF directly to the FDA.

The Applicant understands the need for adherence to the specific mandated FDA manufacturing and packaging guidelines that assure the consumer will receive a drug product that is consistently reproducible.

The Applicant will submit specific street and location addresses, all phone and facsimile numbers for all (substance synthesis sites and product manufacturing sites, all appropriate testing sites, and all product packaging and labeling) sites to the NDA.

The Applicant agrees to submit fabrication material information for the proposed change to support the packaging.

All submissions will be translated into English and the reviewing division will be notified of any inspection site information submissions to the FDA.

Linda Ng, Ph.D.
Team Leader, CMC

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/s/

Nancy Halonen
2/18/04 09:45:43 AM
CSO

Linda Ng
2/18/04 09:59:38 AM
CHEMIST

MEMORANDUM OF TELECON

DATE: February 11, 2004

APPLICATION NUMBER: NDA 21-670, Vision Blue (trypan blue) Intraocular Injection, 0.06%

BETWEEN:

Name: Fran Carleton, Operations Manager
Phone: (603) 642-8468
Representing: D.O.R.C International. B.V.

AND

Name: Nancy Halonen, Project Manager
Linda Ng, Ph.D., Team Leader. CMC
Yong de Lu, Ph.D., CMC Reviewer
Representing: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550, HFD-550

SUBJECT: Inadequacy of response to CMC information requests.

The Sponsor was informed of the inadequacy of the response to the recent information request by the CMC reviewer.

The Sponsor was given the following advice regarding the submission of upcoming information requests as follows:

1. The submission should be an amendment to the NDA, not a revision of the NDA, but a complete separate response to each question that is asked. Each amendment that is submitted to the Agency should be accompanied by a form 356h, and be dated, and the section that states "type of submission" should be checked in the appropriate box: amendment to a pending application, or any of the other selections that may apply. The submissions will be coded and tracked in our document room to help the Applicant and Agency for references in discussion of issues identify when more clarity is needed from an identified amendment submission.
2. Each question that the Agency identifies with a number should be addressed with a separate definitive response. There should be no pooling of answers in a group
3. Please submit complete drug substance manufacturing site information, do not send literature as reference. How and where is the drug actually manufactured?

4. Please submit data to support a conclusion, for example: the stability of the drug substance and the drug product needs stability data to support the expiration date and the specification.
5. To speed up the review process, you can expect further information requests from the CMC reviewer in the near future.
6. The Division is committed to work with the Applicant throughout the review process and the Applicant should feel free to contact us at anytime for clarification or assistance.

A teleconference between _____, Regulatory Affairs, and Dr. Menz, CMC Development, D.O.R.C., International, and the HFD-550 Reviewing Chemists has been scheduled for Friday, February 13th, to continue clarify the requirements for an acceptable NDA submission.

151

Linda Ng, Ph.D.
Team Leader, CMC

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/s/

Nancy Halonen
2/17/04 06:35:24 AM
CSO

Linda Ng
2/17/04 09:05:16 AM
CHEMIST

RECORD OF TELEPHONE CONVERSATION	DATE: 09-02-04
<p>Background: Irma Rivera, Program specialist from International Operations Group of FDA clarified in an e-mail dated 2/9/04 that that the manufacturing site for the drug substance, Trypan blue — is not — as claimed in the NDA. Irma stated that — is not involved in the manufacture of Trypan blue — They appear to be a supplier of laboratory equipment to other companies, and they also conduct some testing.</p> <p>Content: The following telephone call was made by Linda Ng and myself to clarify some issues.</p> <p>1. Fran of Dutch Ophthalmic admitted that the manufacturing site for the drug substance has been changed recently and she committed that she will contact the applicant immediately and forward the current manufacturer information to Nancy Halonen as early as possible. We requested that they confirmed that all their sites and information are accurate.</p> <p>The following detailed information should be provided.</p> <ul style="list-style-type: none"> Names, and addresses of manufacturing site, release testing site and stability testing site for the drug substance Trypan blue — Names and addresses of manufacturing site, release testing site, packaging site, labeling site and stability testing site for the drug product, Vision Blue™, 0.06%. Contact person's name, telephone number and fax number for all above sites <p>2. Fran stated that some changes have been made to the packaging. That is from — syringe</p>	<p>NDA: 21-670</p> <hr/> <p>Initiated by: Applicant _____ FDA <u>X</u></p> <p>Made : by phone <u>X</u> in person _____ by Fax _____</p> <hr/> <p>PRODUCT: Vision Blue, 0.06%</p> <hr/> <p>FIRM: D.O.R.C. Intl. B.V.</p> <hr/> <p>NAME & TITLE: Fran Carleton, Operation Manager of Dutch Ophthalmic, USA. (US Agent) Phone: (603)-642-8468</p> <p>cc:</p>

Signature: Yong-de Lu, Ph.D.	Division: HFD-550/830
---------------------------------	--------------------------

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/s/

Yong-De Lu
2/10/04 02:42:46 PM
CHEMIST

Linda Ng
2/10/04 03:29:53 PM
CHEMIST

Memorandum of Record

E-mail request sent to Sponsor on February 9, 2004.

Good morning Fran,

Our International Operations Group has attempted to contact —
— in order to schedule an inspection. The firm says they are not involved in the
manufacture of NDA 21-670 (Vision Blue).

Please provide more information on the role of this facility with this NDA. Until the involvement of
this facility with Vision Blue is resolved, we cannot attempt to schedule an inspection.

Thank you for your attention to this request,
Nancy

CDR Nancy M. Haionen
Regulatory Health Project Manager
FDA/CDER/ODE V

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/s/

Nancy Halonen
2/9/04 08:49:30 AM
CSO

Memorandum to Record
Dated 2-9-04
Email information request sent to Sponsor

Good morning Fran,

I have one correction/clarification to make in the information request regarding
— The firm says they are not involved in the manufacture of the drug
substance trypan blue — for NDA 21-670 (Vision Blue).

Please provide more information on the role of this facility with manufacture of the drug substance
trypan blue.

Thank you for your attention to this request,
Nancy

CDR Nancy M. Halonen
Regulatory Health Project Manager
FDA/CDER/ODE V

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/s/

Nancy Halonen
2/9/04 10:13:59 AM
CSO

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 22, 2004

NDA#: 21-670

NAME OF DRUG: Vision Blue
(Trypan Blue)
0.06%

NDA HOLDER: Pharmacia Corporation

I. INTRODUCTION:

This consult was written in response to request from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), for assessment of the proprietary name, Vision Blue, regarding potential name confusion with other proprietary and established drug names. Container labels, carton and insert labeling was not submitted for review.

PRODUCT INFORMATION

Vision Blue tissue staining agent is a sterile, _____ solution of trypan blue. Vision Blue is intended for use as an aid in ophthalmic surgery _____ . It is used primarily for staining/rendering visible the frontal lens capsules thereby simplifying making, and limiting the risk of tearing the capsulorhexis. Vision Blue is _____ syringe to which a thin blunt cannula is attached. The procedure is performed, using a slight modification of the routine phaco-emulsification procedure. In order to prevent water-like dilution of Vision Blue, an air bubble is injected into the frontal eye chamber. Vision Blue is then carefully applied to the frontal lens capsula. The frontal eye chamber is next irrigated in order to remove any excess colourant, after which it is injected with a visco-elastic solution. The procedure can now continue as a routine phaco-emulsification procedure. Vision Blue is available in sterile _____ .

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On Original*

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Vision Blue 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 Text and Image Database was also conducted.⁴ The Saegis⁵ 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. No prescription analysis studies were done for Vision Blue as this product will only be used in an operating room and prescriptions for patient use are unlikely to be written.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vision Blue. Potential concerns regarding drug marketing and promotion related to the proposed names 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 did not identify any proprietary name as having the potential for confusion with Vision Blue.
2. DDMAC finds the proprietary name, Vision Blue, unacceptable from a promotional perspective.

B. PRESCRIPTION ANALYSIS STUDY

No prescription analysis studies were done for Vision Blue as this product will only be used in an operating room and prescriptions for patient use are unlikely to be written.

C. PHONETIC AND ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

³ The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

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

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA.

D. SAFETY EVALUATOR RISK ASSESSMENT

No proprietary names were identified by the expert panel or via POCA as having the potential to look or sound similar to Vision Blue. Additionally, through independent analysis, no names were identified as having potential look and sound similarity to the proposed proprietary name.

III. **LABELING, PACKAGING, AND SAFETY RELATED ISSUES**

DMETS requests submission of the container labels, carton and insert labeling for review and comment when available.

IV. **RECOMMENDATIONS**

- A. DMETS has no objections to the use of the proprietary name Vision Blue. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS requests submission of the container labels, carton and insert labeling for review and comment when available. As of January 28, 2004, no new labels have been submitted.
- C. DDMAC finds the proprietary name, Vision Blue, unacceptable from a promotional perspective.

/

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Linda Y. Kim-Jung, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

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

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/s/

Linda Kim-Jung
2/3/04 03:17:23 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/3/04 03:35:21 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/4/04 07:22:29 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
2/4/04 02:51:44 PM
DRUG SAFETY OFFICE REVIEWER

4 Pages Redacted of
Deliberative Process
§ 552(b)(5)

MEMORANDUM

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

DATE: October 30, 2003

TO: Carmen DeBellas
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products,
HFD-550

FROM: Patricia Stewart
Division of Medical Imaging and radiopharmaceutical Drug Products, HFD-160

SUBJECT: Transfer of NDA 21-670
Trypan Blue Dye for ocular tissue staining

In the line with the ORM policy of placing administrative responsibility of NDAs within the Division that reviews the principal clinical research activity of the drug, we are forwarding the attached NDA for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-827-7496.

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/s/

Carmen DeBellas
10/30/03 03:06:58 PM

NDA FILEABILITY CHECKLIST

NDA Number: 21-670

Applicant: Dutch Ophthalmic Research Center,
International

Stamp Date: 29-Oct-2003

Drug Name: VisionBlue™ (Trypan Blue) 0.06%

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

Although data are missing from certain CMC sections of the NDA, sufficient information have been submitted to allow for a preliminary assessment of the adequacy of the application. Due to the importance of the drug product, chemistry will work with the sponsor to address the deficiencies found in the application. Although the following list does not summarize the specific deficiencies in detail, those deficiencies were faxed to the sponsor on December 8, 2003. A summary of the deficiencies will be conveyed in the 74-day letter.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?		✓	
2	Is the section indexed and paginated adequately?	✓		No page number necessary for this tiny submission
3	On its face, is the section legible?		✓	Did not follow FDA Guidance
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	✓		No CFNs and registration numbers were provided for all facilities. Street address provided
5	Is a statement provided that all facilities are ready for GMP inspection?	✓		
6	Has an environmental assessment report or categorical exclusion been provided?	✓		
7	Does the section contain controls for the drug substance?		✓	Only COA and one page copy of _____ and safety data sheet provided by _____ no manufacturing description
8	Does the section contain controls for the drug product?		✓	No description for manufacturing and in-process control provided, only COA
9	Has stability data and analysis been provided to support the requested expiration date?		✓	_____ expiry for the drug substance, supported by _____ not stability indicating; no drug product data are presented.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			No IND filing, no pre-NDA meeting held.
11	Have draft container labels been provided?	✓		
12	Has the draft package insert been provided?	✓		
13	Has an investigational formulations section been provided?		✓	
14	Is there a Methods Validation package?		✓	Analytical methods used have been briefly described but no actual methods validation information has been provided.
15	Is a separate microbiological section included?		✓	Minimal microbiological information has been provided.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Team Leader: Linda Ng, Ph.D.

Date: 12/22/03

Acting Deputy Division Director: David Lin, Ph.D.

Date: 12/22/03

cc:

Original NDA 21-670

HFD-550/Division File

HFD-820/Chem/YLu

HFD-550/PM/NHalonon

HFD-550/DivDir/WChambers

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/s/

Linda Ng
12/22/03 05:03:10 PM
CHEMIST
Filing for reviewer, Yong de Lu

David T. Lin
12/22/03 05:49:06 PM
CHEMIST
I concur.

12/24/03

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-670
Trade Name: Vision Blue
Generic Name: trypan blue
Strengths: 0.06%

Applicant: Dutch Ophthalmic Research Center, International
Date of Application: October 24, 2003
Date of Receipt: October 27, 2003
Date clock started after UN: N/A
Date of Filing Meeting: November 25, 2003
Filing Date: December 26, 2003
Action Goal Date : March 24, 2004

Indication requested: to provide contrast to aid in visualization of the anterior lens capsule when performing the capsulorhexis in cataract surgery.

Type of Original NDA: (b)(1) _____ (b)(2) **X** _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: **Priority Application**
Resubmission after withdrawal? NO Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) _____

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

Form 3397 (User Fee Cover Sheet) submitted: **YES** **NO**
User Fee ID # N/A (waived)
Clinical data? **NO X** **No NDAs referenced, multiple European peer reviewed articles referencing previous clinical studies, most in English, some in German and French.**

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES X **NO**
If yes, explain: This is an NME, never marketed in the US. It may receive 5 years of exclusivity.

Does another drug have orphan drug exclusivity for the same indication? **YES** **NO**

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
 “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES NO
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

The Applicant claims these forms are not relevant since the NDA is supported by peer-reviewed articles referencing previous clinical studies authored by clinicians not invested in the NDA product.

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **None Listed**

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

- Pre-NDA Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment?
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to Nancy Sager (HFD-357)?

	See CMC review	
	YES	NO
	YES	NO
- Establishment Evaluation Request (EER) submitted to DMPQ?
See CMC review
- If a parenteral product, consulted to Microbiology Team (HFD-805)?

<u>YES</u>	NO
------------	----

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: **Peer-reviewed articles were submitted. No referenced NDAs noted.**
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **N/A**
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

	YES	<u>NO</u>
--	-----	-----------
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

	<u>N/A</u>	
	YES	NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

	<u>N/A</u>	
	YES	NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

X 21 CFR 314.50(i)(1)(i)(A)(4): **The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.**

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

 21 CFR 314.50(i)(1)(ii): No relevant patents.

 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

 Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

N/A

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

OR

N/A	IND # _____	NO
-----	-------------	----

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A	YES	NO
-----	-----	----

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-25-03

BACKGROUND:

VisionBlue, which is a biological stain, obtained CE approval as a medical device Class IIa in 1999. It is currently marketed in 30 countries and has applications for marketing pending in the United State, —

ATTENDEES:

Brian Harvey, Wiley Chambers, William Boyd, Jennifer Harris, Lucious Lim, Lori Gorski, Carmen DeBellas, Michael Puglisi, Raphael Rodriguez, Dennis Bashaw, Stan Lin, Linda Ng, Peter H. Cooney, Conrad Chen, Josie Yang, Yong de Lu, Nancy Halonen

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Wiley Chambers
Pharmacology:	Conrad Chen
Chemistry:	Yong de Lu
Microbiology, sterility:	Peter Cooney
Regulatory Project Management:	Nancy Halonen
Other Consults: DDMAC, ODS	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain: **Many peer-reviewed referenced articles are in German or French. The Company will address these concerns immediately.**

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY FILE X REFUSE TO FILE _____

STATISTICS FILE X REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X REFUSE TO FILE _____

- Biopharm. inspection needed: waiver only NO YES

PHARMACOLOGY FILE X REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE X REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION: N/A
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

X Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. Document filing issues conveyed to applicant by January 9, 2004.

 Nancy M. Halonen
Regulatory Project Manager, HFD-

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/s/

Nancy Halonen
12/29/03 11:13:48 AM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: October 27, 2003	DESIRED COMPLETION DATE: December 27, 2003 PDUFA DATE: April 27, 2004	ODS CONSULT #: 03-0298
---	---	-------------------------------

TO: Brian Harvey, M.D.
Acting Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Nancy M. Halonen
Project Manager
HFD-550

PRODUCT NAME: Vision Blue (Trypan Blue) 0.06% NDA: 21-670	Manufacturer: Pharmacia Corporation
---	---

SAFETY EVALUATOR: Linda Y. Kim-Jung, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Vision Blue. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS requests submission of the container labels, carton and insert labeling for review and comment when available. As of January 28, 2004, no new labels have been submitted.
3. DDMAC finds the proprietary name, Vision Blue, unacceptable from a promotional perspective.

/s/

/s/

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-670

D.O.R.C. International B.V.
Attention: Fran Carleton
Operations Manager
One Little River Road
P.O.Box 968
Kingston, NH 03848

Dear Ms. Carleton:

Please refer to your October 24, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vision Blue (trypan blue intraocular solution) 0.06%

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 26, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Regulatory:

1. Please provide a new form 356h and a new Debarment Certification with US agent signature.
2. Please ensure that all new submissions to the NDA are provided in English and provide English translation for the parts of the NDA that were previously submitted in a foreign language.

Clinical:

3. The literature articles submitted are incomplete. Please submit complete versions of the cited references.

Microbiology:

4. Please provide a complete description of the sterilization process for the product. Specific details were provided to you in the FAX dated November 25, 2003.

Additional explanations of the information and data required can be found on the CDER website under Guidances. Specifically, the 1994 *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* which can be accessed at www.fda.gov/cder/guidance.

Chemistry, Manufacturing, and Controls:

5. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to assure its identity, strength, quality, purity, and stability. Specifically, the deficient or missing information with respect to the following should be provided:
 - a. characterization of the drug substance,
 - b. manufacturing of the drug substance and the drug product,
 - c. description of the container/closure system for the drug substance and the drug product,
 - d. specification of the drug substance and the drug product, and
 - e. stability of the drug substance and the drug product.

Please provide full descriptions of the drug substance and the drug product. Specific details were provided to you in the FAX dated December 8, 2003. The appropriate guidances are accessible at www.fda.gov/cder/guidance.

Labeling:

6. The proposed labeling does not conform to the labeling regulation 21 CFR 201.57. Please submit revised labeling which conforms to 21 CFR 201.57.

We are providing the above comments to give you preliminary notice of potential 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.

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley 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

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/s/

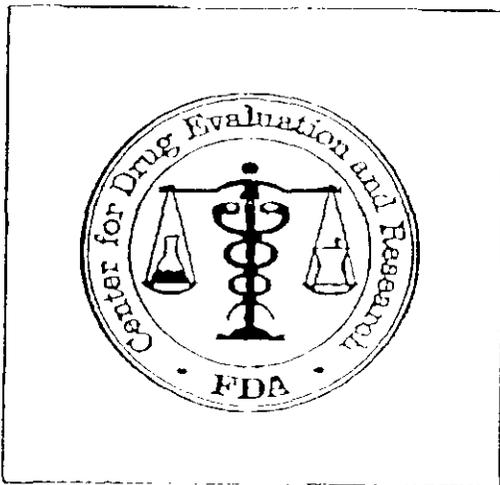
Wiley Chambers
12/29/03 12:12:40 PM

*** TX REPORT ***

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CONNECTION ID DUTCH OPHTHALMIC
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RESULT OK

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From: Yongde Lu, Ph.D.

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

Phone 301-827-2040

Fax 301-827-2531

Date: 12/8/03

To: Name Fran Carleton
Company Dutch Ophthalmic, USA
City Kingston State NH
Phone # 603-642-8468

FAX # 603-642-8465

Number of Pages (INCLUDING COVER PAGE) 5

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

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immediately by telephone and return it to us at the above address by mail. Thank you.

Additional message:

December 8, 2003

NDA 21-670

VisionBlue®

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. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per 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 SUBSTANCE

1. Please provide a full description of the physical and chemical characteristics of the drug substance. These may include name (USAN name, chemical name, code number); description (e.g., appearance, color, physical state); molecular formula and molecular weight; structural formula (including ionic state if applicable); solution pH; dissociation constant(s); melting point etc.
(reference to FDA Guideline: *Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*)
2. The elucidation of structure (e.g., the data and its interpretation) should be submitted based on appropriate physical and chemical test results. These may include the following: elemental analysis; mass spectrometry (MS); nuclear magnetic resonance (NMR), ultraviolet (UV), infrared (IR) spectroscopy and chromatographic profile. (reference to FDA Guideline: *Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*)
3. Information concerning drug substance impurities should be provided. These may include following.
 - organic, inorganic impurities and residual solvents
 - process impurities and degradation impurities
 - impurities present in starting materials that are carried over to the drug substance
 - impurities observed by HPLC analysis being presented as identified and unidentified

- identified impurities supported by structural characterization data.
(reference to ICH guideline *Q3A Impurities in New Drug Substances and Q3C Impurities: Residual Solvents*)
4. A complete description of the manufacturing process, from starting material(s) to the bulk new drug substance, should be submitted. These may include the following:
 - starting materials, solvents, reagents and auxiliary materials
 - narrative description of the manufacturing process including purification of the drug substance(reference to FDA Guideline: *Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*)
 5. A description of the preparation and characterization of reference standards for both drug substance and impurities should be provided. A submission of Certificates of Analysis (CoA) for reference standards is recommended.
(reference to FDA Guideline: *Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*)
 6. Please submit a description of the release control on the drug substance, including:
 - a proposed specification (list of tests, references to analytical procedures, and acceptance criteria)
 - proposed analytical procedures
 - validation data of proposed analytical methods
 - batch analyses
 - justification of specifications(reference to ICH guideline *Q6A Specification: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substance and FDA Guideline: Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*)
 7. Please submit a description of the container system that will be used to package the drug substance.
(reference to FDA Guideline: *Container Closure Systems for Packaging Human Drugs and Biologics, 1999*)
 8. On page 7 of 21 in the paragraph of drug substance stability, Appendix B5 and B6 were cited for reference. However, in both Appendix B5 and B6 the testing articles are 'Vision Blue — (drug product). Please clarify.
 9. Please provide the stability data for the drug substance. (reference to ICH *Q1A(R2) Stability Testing of New Drug Substances and Products*)
 10. Alternatively, the information listed above may be provided in a DMF (reference to FDA Guideline: *Drug Master Files, 1989 and Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substance, 1987*). If a DMF has been

filed, please provide a letter of authorization (LOA) from the DMF holder to authorize FDA to reference the DMF in support of the NDA.

DRUG PRODUCT

10. Please provide a list of components, including all substances and in-process materials used in producing a finished drug product, and state the quality designation or grade for each material (e.g., ACS, USP, NF, etc.)
(reference to FDA Guideline: *Submitting Documentation for the Manufacturing of and Controls for Drug Products, 1987*)
12. A batch formula should be submitted, including a complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product.
(reference to FDA Guideline: *Submitting Documentation for the Manufacturing of and Controls for Drug Products, 1987*)
13. Specifications or certificates of analysis for inactive components should be provided.
(reference to FDA Guideline: *Submitting Documentation for the Manufacturing of and Controls for Drug Products, 1987*)
14. Please submit a detailed description of the manufacturing, packaging process and in-process control for representative batch of drug product.
(reference to FDA Guideline: *Submitting Documentation for the Manufacturing of and Controls for Drug Products, 1987*)
15. Please submit a specification and its justification for the drug product, including acceptance criteria, testing methods and reference operating procedures.
(reference to ICH guideline *Q6A Specification: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substance* and FDA Guideline: *Submitting Documentation for the Manufacturing of and Controls for Drug Products, 1987*)
16. Please submit a narrative description and clear drawing for the container/closure system for the drug product. In the container label, it is stated that "Visionblue® 0.5 mL, packaged in - syringe", nevertheless, in the packaging section of the packaging insert, it is said that "Visionblue® is available in sterile - . Please clarify.
(reference to FDA Guideline: *Container Closure Systems for Packaging Human Drugs and Biologics, 1999*)
17. On page 7 of 21 in paragraph of stability and Appendix B5 and B6, please clarify and explain" - . Since - assay methods are not stability indicating, a stability indicating method should be used to assay the drug substance and related impurities, such as HPLC method.

18. Please include specific stability topics such as stability study protocols, testing conditions, expiration dating, tabular stability data, and post approval stability commitment in the drug product stability section. Stability data for the proposed tests should be submitted to support the expiration dating period.
(reference to ICH guideline *Q1A stability Testing of New drug Substances and Products* and FDA Guideline: *Submitting Documentation for the Stability of Human Drugs and Biologics, 1987*)

APPEARS THIS WAY
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/s/

Yong-De Lu
12/8/03 04:46:52 PM
CHEMIST
Information Requests

Linda Ng
12/9/03 05:45:55 PM
CHEMIST
No action needed by PM

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: Fran Carleton, Regulatory Affairs

From: Nancy M. Halonen

Fax: (603) 642-8465

Fax: (301) 827-2531

Phone: (603) 642-8468

Phone: (301) 827-2019

Pages: (1 incl. cover)

Date: November 28, 2003

Re: Information request for NDA 21-670 (Vision Blue)

Urgent Review Only Please Comment Please Reply Please Recycle

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Good afternoon Fran,

I have 3 requests to make of you today:

1. The 356h form requires both the foreign applicant and the U.S. agent signature. The current 356h has only the foreign applicant signature. Please submit a 356h with both the foreign applicant and U.S. agent signatures.
2. The Debarment Certification must have both foreign and U.S. agent signatures as well, and currently, only the foreign applicant signature has been provided.
3. Please provide the complete cited reference for the articles found in Appendix T.
Please submit these responses as amendments to the NDA.

Also, please note that all new submissions to the NDA must be provided in English. Please remember to provide English translation to the parts of the NDA that were already submitted in a foreign language.

Thank you in advance for your assistance with the information requests.

Regards,

Nancy

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/s/

Nancy Halonen
11/28/03 11:00:05 AM
CSO

William Boyd
11/28/03 11:45:52 AM
MEDICAL OFFICER

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: Ms. Fran Carleton, Regulatory Affairs

From: CDR Nancy M. Halonen

Fax: (603) 642-8465

Fax: (301) 827-2531

Phone: (603) 642-8468

Phone: (301) 827-2019

Pages: (4 incl. cover)

Date: November 25, 2003

Re: Information request for NDA 21-670 (Vision Blue)

Urgent Review Only Please Comment Please Reply

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Good afternoon Fran,

Here is a Microbiology information request. You can expect a Chemistry information request in the near future.

Please note that all future information requests will require a response with 4 copies, each including a form 356h to accompany them. This is to ensure that all the reviewers have a copy of needed information to expedite a review.

Thank you in advance for your assistance with the information requests.

Feel free to call me if you have any concerns.

Regards,

Nancy

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3

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Nancy Halonen
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-670

D.O.R.C. International B.V.
Attention: Fran Carleton
Operations Manager
One Little River Road
P.O.Box 968
Kingston, NH 03848

Dear Ms. Carleton:

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:	Vision Blue (trypan blue) Intraocular Injection 0.06%
Review Priority Classification:	Priority (P)
Date of Application:	October 24, 2003
Date of Receipt:	October 27, 2003
Our Reference Number:	NDA 21-670

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 December 26, 2003 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be April 24, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

NDA 21-670
Page 2

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:

Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
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
Attention: Document Room, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

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

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/s/

Carmen DeBellas
11/5/03 03:48:14 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

SEP 26 2003

Food and Drug Administration
Rockville MD 20857

Fran Carleton
Dutch Ophthalmic, USA, Inc.
One Little River Road
P.O. Box 968
Kingston, NH 03848

RE: Dutch Ophthalmic, USA, Inc., Small Business Waiver Request 2003.054 for Vision Blue (trypan blue), NDA 21-670

Dear Ms. Carleton:

This responds to the June 13, 2003, letter from Frank Ruseler and the September 15, 2003, facsimile to Beverly Friedman of my staff requesting a waiver of the human drug application fee for the new drug application (NDA) 21-670 for Vision Blue (trypan blue), under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.054). For the reasons described below, the Food and Drug Administration (FDA) grants Dutch International, b.v., and Dutch Ophthalmic, USA, Inc.'s (DOUSA's) request for a small business waiver of the application fee for NDA 21-670, Vision Blue (trypan blue).

According to your waiver request, DOUSA is a small business with — employees and several affiliates. You note that NDA 21-670 will be DOUSA's first application submitted to FDA for review under section 505(b) of the Act.

Under section 736(d)(3)(B) of the Act,² a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate³ submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

¹ 21 U.S.C. 379h(d)(1)(D).

² 21 U.S.C. 379h(d)(3)(B).

³ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

APPEARS THIS WAY
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Dutch Ophthalmic, USA, Inc.

Waiver Request # 2003.054

Page 2

FDA's decision to grant DOUSA's request for a small business waiver for its NDA 21-670 is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated July 18, 2003, that DOUSA has fewer than 500 employees including its affiliates: DORC International b.v., DORC Scandinavia AB, DORC Frans S.A.R.L., DORC Nederland b.v., Ophthalux b.v., Markerik Beheer b.v., MicroVision Inc., Eye Technology Ltd., and Medical Instrument Design.

Second, according to FDA records, the marketing application for Vision Blue is the first human drug application, within the meaning of the Act, to be submitted to FDA by DOUSA or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-670 is granted, provided that FDA receives the marketing application for Vision Blue no later than July 18, 2004, 1 year after the effective date of the size determination made by SBA. Please include a copy of this letter with your application.

If FDA refuses to file the application or DOUSA withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, DOUSA should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for DOUSA's NDA 21-670.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,

51

Jane A. Axelrad /

Associate Director for Policy

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane (HF-7)
Room 4B-44
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

April 14, 2003

Jonathan S. Kahan, Esq.
Hogan & Hartson, LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

RE: Request for Reconsideration
VisionBlue® Ophthalmic Solution
Our File: RFD 2000.009

Dear Mr. Kahan:

The Food and Drug Administration (FDA) has completed its review of the May 3, 2002, Request for Reconsideration you submitted on behalf of Dutch Ophthalmics, USA. Your request seeks reconsideration of our July 19, 2000 decision that VisionBlue is a drug rather than a device. For the reasons described below, we affirm our decision that VisionBlue is a drug.

VisionBlue consists of trypan blue — sodium chloride — Trypan blue is a vital dye; it stains dead cells but not live cells. The product is intended to be used in cataract surgery where the surgeon removes the patient's natural lens. The lens has a thin covering known as the lens capsule. To access the lens, the surgeon must remove the front portion of the lens capsule. VisionBlue is placed onto the anterior lens capsule and stains it blue, thus making it easier for the surgeon to see the lens capsule and remove it.

During cataract surgery, the patient lies face up on the table. An incision is made in the cornea with a surgical knife. A cannula is placed through the incision and the anterior chamber is filled with air. The purpose of the air bubble is to minimize dilution of VisionBlue by aqueous fluid. VisionBlue is applied as a drop through the cannula directly onto the lens capsule. The lens capsule is quickly stained blue, and the anterior chamber is irrigated to remove excess colorant. The surgeon can then visually identify and remove a portion of the anterior lens capsule. During surgery, the eye is continually flushed with balanced salt solution, thereby removing any excess VisionBlue. Any residual VisionBlue remaining after cataract surgery is removed through normal aqueous and tear production. Dutch Ophthalmics presented data demonstrating that they were unable to find residual colorant is found in the eye 12 months after surgery.

On May 16, 2000, Dutch Ophthalmics submitted a Request for Designation (RFD) requesting classification of VisionBlue as a device. This RFD stated, among other things, that the staining of the lens capsule is achieved by "passive adherence to collagenous tissues," whereas "living cells do not actively take up VisionBlue and remain

Dutch Ophthalmics, USA
April 14, 2003
Page 2

unstained...." FDA's initial designation letter, dated July 19, 2000, concluded that VisionBlue is a drug, stating that we were not aware of any products lawfully marketed as medical devices that exploit a differential staining property similar to the one described for VisionBlue.

On May 3, 2002, Dutch Ophthalmics requested reconsideration of the initial designation decision. The essence of the request for reconsideration is Dutch Ophthalmics' assertion that the agency erred in its conclusion that VisionBlue exploits the differential staining characteristics of trypan blue. According to the request for reconsideration, VisionBlue achieves its primary intended purpose by physical intercalation with the anterior lens capsule's three-dimensional collagenous structure, and not by either chemical or metabolic action. The request for reconsideration explains the company's intercalation theory. It states that because of the

large size of the dye molecule relative to the open three-dimensional structure of collagen, trypan blue molecules can become physically entangled within and temporarily mark the tissue.

The request for reconsideration also notes that the lens capsule is completely devoid of cells, living or dead, and then asserts that differential staining is neither necessary nor even possible for VisionBlue's intended use. Therefore, according to the request for reconsideration, Dutch Ophthalmics claims that VisionBlue meets the definition of a device contained in 21 U.S.C. § 201(h).

Moreover, according to the request for reconsideration, the classification of VisionBlue as a drug creates a significant disparity between VisionBlue and other ophthalmic surgical markers containing vital dyes (e.g., gentian violet and methylene blue). According to the request for reconsideration, the

use of dyes as ophthalmic surgical markers is so uncontroversial that FDA long ago classified them as devices *exempt* from the 510(k) premarket notification process (21 CFR § 886.4570).... In contrast, FDA's designation of VisionBlue ... as a drug means that this functionally indistinguishable product will be regulated under the new drug application (NDA) process.

The request for reconsideration states that this regulatory scheme would impose a significant and unfair competitive disadvantage on Dutch Ophthalmics with no articulated scientific basis.

We have reviewed all the information you submitted, met with you, and consulted with officials in the Center for Drug Evaluation and Research (CDER), the Center for

Devices and Radiological Health (CDRH) and the Office of Chief Counsel.¹ For the reasons described below, we affirm our previous determination and are classifying VisionBlue as a drug.

First, VisionBlue meets the definition of a drug contained in the Federal Food, Drug, and Cosmetic Act at 21 U.S.C. 321(g). It is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man; and/or an article intended to affect the structure or any function of the body.

Second, VisionBlue has not been shown to achieve its primary intended purpose without chemical action within the body. Thus, although VisionBlue clearly meets the definition of a drug, it has not been shown that it meets the definition of a device.

The request for reconsideration asserts that VisionBlue stains the lens capsule by physical intercalation, and describes intercalation as the large VisionBlue molecules becoming physically entangled within the three dimensional structure of collagen and temporarily marking the tissue.² FDA believes that the science of intercalation is new

¹ On February 13, 2002, officials from CDRH, CDER, Office of Chief Counsel, and the Ombudsman's Office met with representatives of Dutch Ophthalmics to discuss the feasibility of the company submitting a Request for Reconsideration. Dutch Ophthalmics submitted additional information via electronic mail on September 24, 2002, and October 28, 2002. Numerous telephone conversations also took place between counsel for Dutch Ophthalmics and the Ombudsman's Office while this Request for Reconsideration was being reviewed.

² The Request for Reconsideration contains a detailed statement of Dutch Ophthalmics' conclusion that VisionBlue does not stain the lens capsule through chemical action. Among other things, this statement concludes that VisionBlue could not stain the lens capsule by hydrogen bonding because, when solubilized in an aqueous solution at a neutral pH, VisionBlue does not contain any charged atomic constituents that could serve to either accept or donate hydrogen atoms for the formation of hydrogen bonds. (VisionBlue's pH is 7.4.) A further discussion of the possibility of hydrogen bonding was prompted by a statement in a reference Dutch Ophthalmics submitted with the Request for Reconsideration that dyes such as trypan blue stain "apparently by hydrogen bonding rather than by anionic salt unions as with ordinary cytoplasmic structures..." (Lillie RD, Fullmer HM, (eds): *Histopathologic Technic and Practical Histochemistry*, 4th ed. New York, McGraw-Hill Book Company pp. 140-144.)

The subsequent discussion included an analysis of a study showing that VisionBlue eluted from the lens capsule at the same rate regardless of the pH (pH was altered to range from 4 to 10). The study was designed to determine whether covalent bonding occurred with VisionBlue. Dutch Ophthalmics concluded that since no change in elution time was observed in the study, covalent bonding had not occurred. In response to a question from FDA, the company stated in an e-mail dated October 28, 2002 that the same general conclusion could be inferred with regard to hydrogen bonding. This e-mail reiterated that from Dutch Ophthalmic's perspective, the most important point about hydrogen bonding is that because the pH of the eye and VisionBlue are neutral, and VisionBlue therefore does not contain charged hydrogen molecules, hydrogen bonding cannot be responsible for the staining of the lens capsule.

and imprecise; the current literature is not definitive as to whether the process is physical or chemical. Even if intercalation is a purely physical process, however, it would not be clear that VisionBlue meets the definition of a device because the primary intended purpose of VisionBlue is not simply to stain the lens capsule. The primary intended purpose of VisionBlue is to stain the lens capsule and at the same time, **not** stain the lens.³ It is by staining the lens capsule -- and only the lens capsule -- that VisionBlue enables the surgeon to see the lens capsule and remove it. The inability of VisionBlue to stain the live cells in the lens is likely due to some kind of chemical action.

Dutch Ophthalmics asserts in response that the lens remains unstained not because of the characteristics of VisionBlue, but because of the characteristics of the lens capsule, which physically prevents VisionBlue from coming into contact with the lens. In a telephone conversation, counsel for Dutch Ophthalmics analogized the lens capsule to the shell of a hard boiled egg. When a hard boiled egg is dyed, the egg itself is not dyed because the shell prevents the dye from coming into contact with the egg. In this conception of VisionBlue's mechanism of action, trypan blue's differential staining characteristics would be irrelevant.

We acknowledge that initially the lens capsule could prevent VisionBlue from staining the lens by acting as a physical barrier between VisionBlue and the lens. However, as Dutch Ophthalmics' description of the use of VisionBlue makes clear, some VisionBlue remains in the anterior chamber while the surgeon removes the lens capsule.⁴ In addition, as made clear by the video submitted with the initial RFD, the lens capsule is not removed whole; instead, the surgeon tears strips of the lens capsule away, a piece at a time. At every tear, the surgeon must be able to differentiate between the lens and the lens capsule. It is at this stage, where the lens capsule has been partially removed, and the lens is partially exposed, that the effectiveness of VisionBlue depends on its inability to stain the live cells of the lens. Thus, we conclude that VisionBlue does exploit its differential staining characteristic to accomplish its primary intended purpose.

The information provided to FDA does not explain how VisionBlue stains dead cells and tissue with no cells at all, but does not stain live cells. Nevertheless, we

As explained above, FDA concludes that the intended purpose of VisionBlue is to stain the lens capsule while not staining the lens. Whether or not VisionBlue stains the lens capsule through hydrogen bonding, the agency concludes that the fact that VisionBlue does not stain the non-capsular portion of the lens is due to chemical action of some sort.

³ In a e-mail dated September 24, 2002, counsel for Dutch Ophthalmics stated that the intended use of VisionBlue is to allow the surgeon "to distinguish the lens capsule from the underlying lens mass."

⁴ The initial RFD, dated May 16, 2000, states on page 10 that "During surgery the eye is continually flushed with balanced salt solution, thereby removing any excess VisionBlue. The duration of use is typically the time of surgery, which normally takes place in 30 minutes or less. Any residual VisionBlue is removed through normal aqueous and tear production post surgery."

believe this differential staining characteristic entails chemical action of some kind. Therefore, we conclude that that VisionBlue achieves its primary intended purpose through chemical action within the body. Accordingly, we conclude that VisionBlue has not been shown to meet the definition of a device.

Third, VisionBlue does not fit within the generic type of device "ophthalmic surgical marker" covered by 21 CFR § 886.4570. This classification only applies to medical devices and VisionBlue is a drug. Even if VisionBlue were a device, it would not be covered by this classification. Devices covered by this classification regulation are intended for use in marking the cornea, sclera, or exterior surface of the eye to show where a surgical incision should be made. VisionBlue, in contrast, is applied intraocularly for a very different purpose, as described above. While both VisionBlue and some of the marking pens included in this classification use vital dyes (gentian violet and methylene blue), that does not, by itself, mean that VisionBlue fits within that classification.

Finally, the FDA's decision that VisionBlue is a drug is consistent with past agency decisions. We are aware of no product legally marketed as a device that is intended to mark or dye the inside of the eye. For example, we have previously classified fluorescein strips as a drug. Fluorescein sodium is another vital dye. It is available in ophthalmic strips indicated for staining the anterior segment of the eye when delineating a corneal injury, herpetic lesion or foreign body, or determining the site of an intraocular injury. The fluorescein impregnated strips are placed on the eye until adequate staining is achieved. In the Federal Register of November 8, 1986, fluorescein strips were classified as drugs.

For these reasons (VisionBlue meets the statutory definition of a drug, VisionBlue has not been shown to meet the statutory definition of a device, VisionBlue does not fit within the description of products covered by 21 CFR § 886.4570, and the agency regulates other vital dyes intended for use inside the eye as drugs), we affirm our previous decision and conclude that VisionBlue is a drug.

CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAOPD) will be responsible for the premarket review and regulation of VisionBlue. For further information, contact Lori Gorski, Project Manager, Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, 9201 Corporate Boulevard, HFD-550, Rockville, MD 20850 or at 301-827-2090.

Dutch Ophthalmics, USA
April 14, 2003
Page 6

As you know, you may request supervisory review of this decision under 21 CFR § 10.75. If you have any other questions about this letter, or wish to discuss the matter further with the Ombudsman's Office, please contact me at 301-827-3390.

Sincerely,



Suzanne O'Shea
Product Jurisdiction Officer

cc: Lori Gorski

Office of the Ombudsman
5600 Fishers Lane (HF-7)
Room 14B-03
Rockville, MD 20857

July 19, 2000

Re: Request for Designation
Trypan Blue Ophthalmic Surgical Marker
Our File: RFD 2000.009

Dear Ms

The Food and Drug Administration has completed its review of the request for designation, which you submitted on behalf of Dutch Ophthalmics, USA. The request was filed by this office on May 24, 2000. By mutual agreement, the designation deadline for the request was extended to permit full consideration of the issues raised.

The request seeks jurisdictional classification and assignment of Dutch Ophthalmics' VisionBlue Ophthalmic Surgical Marker (VisionBlue). VisionBlue is a trypan blue dye (0.06%) intended for use in cataract surgery. The product formulation is fully described in the request; the product description is incorporated here by reference.

VisionBlue is intended for use to provide "contrast to aid visualization of the capsule when performing the capsulorhexis in mature cataract surgery." According to the request for designation, the product "acts by physically staining the anterior capsule, which renders the capsule visible by providing contrast to the underlying crystalline lens."

Your request recommends that primary review responsibility for VisionBlue be assigned to FDA's Center for Devices and Radiological Health (CDRH). In addition, you suggest that the product be regulated under the medical device provisions of the Federal Food, Drug, and Cosmetic Act (the "Act"). The request argues that VisionBlue is appropriately regulated as a medical device because (1) the product has the physical attributes like those described in the device classification regulation for ophthalmic markers (21 CFR 886.4570); and (2) the product performs a device function. Further, you argue that a number of companies are lawfully marketing ocular and scleral markers as medical devices.

July 19, 2000
Page 2

We have carefully considered the information provided in the request, reviewed the pertinent provisions of the Intercenter Agreement (ICA) between CDRH and the Center for Drug Evaluation and Research (CDER), and discussed the issues with senior officials in both centers. Based on our review, we are designating CDER as the agency component with primary jurisdiction for the premarket review and regulation of the product. VisionBlue will be reviewed and regulated under the new drug provisions of the Act, 21 U.S.C. 355. Any clinical investigations of VisionBlue should be conducted under an investigational new drug application in accordance with 21 CFR Part 312.

Our decision is consistent with the jurisdictional classification and assignment of other stains and dyes intended for use in cataract surgery to assist in the visualization of the capsule. The decision reflects our understanding that the mechanism of action of the product exploits differences in the staining properties of the dye. Specifically, as you note in your request, the staining of the capsule is achieved by "passive diffusion into dead cells or passive adherence to collagenous tissues," whereas "living cells do not actively take up VisionBlue and remain unstained . . ." (Request for Designation at page 9.) We are not aware of any products lawfully marketed as medical devices with a similar mechanism of action.

CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products will be primarily responsible for the premarket review and regulation of VisionBlue. For further information about submission requirements, contact Leslie Vaccari, Supervisory Project Manager, at 301-827-2090.

We understand that you may want to request reconsideration of this jurisdictional decision. Please contact Tracey Forfa, of this office, for guidance on the procedures for requesting reconsideration, or if you want to arrange a meeting to discuss the matter. She can be reached at 301-827-3390.

Sincerely yours,

/s/

Steven H. Unger
Product Jurisdiction Officer

cc: Leslie Vaccari

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cc: Leslie Vaccari

bcc:

HF-7	RFD 0.009/TF Chron/SU Chron/notebook
HFM-4	Lard
HFD-100	Morrison
HFZ-404	Berk

Finalized 7/19/00 - kvw