

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-670

APPROVABLE LETTER(S)



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 October 24, 2003, new drug application (NDA), received October 27, 2003, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vision Blue (trypan blue intraocular solution) 0.06%. Please be advised that the correct PDUFA User Fee Goal Date is April 27, 2004, based on the receipt date of the application.

We acknowledge receipt of your submissions dated December 31, 2003, and January 29, February 5, 18, and 23, and March 8 (two), 2004.

We also acknowledge receipt of your submission dated April 5, 2004. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter. It is not necessary to resubmit any information that has already been received by the Agency.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to provide response for the following issues.

Regulatory

1. To complete your application, the following forms need to be submitted. They are available at the following website: <http://forms.psc.gov/forms/FDA>.
 - a. Submit a completed FDA Form 3542a (Patent Information Submitted with the Filing of a NDA, Amendment or Supplement).
 - b. Submit a completed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators).
 - c. Submit a completed FDA Form 3455 (Disclosure: Financial Interests and Arrangements with Investigators).

Drug Substance

The methods to be used in, and the facilities and controls used for manufacturing, processing, packaging, and holding of the drug substance are inadequate to assure its identity, strength, quality, purity, and stability. Specifically, the following information and data must be submitted:

2. Provide a full description of the physical and chemical characteristics of the drug substance. These should include name (USAN name, code number) and description (e.g., solution pH, dissociation constant(s), melting point, etc.).
3. Submit the elucidation of structure (e.g., the data and its interpretation) based on appropriate physical and chemical test results. These should include elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR), ultraviolet (UV), infrared (IR) spectroscopy or chromatographic profile.
4. Submit a flow chart of synthesis from the starting material(s) to the drug substance. In addition, provide a narrative description of the manufacturing processes to cover the starting materials, solvents, reagents, and auxiliary materials.
5. Provide a description of the preparation and characterization of the reference standard for the drug substance. In addition, data to support the quality and purity of the reference standard should be submitted.
6. Provide data for the drug substance impurities to include organic, inorganic impurities and residual solvents, process impurities and degradation impurities, and impurities present in starting materials that are carried over to the drug substance. Impurities observed by HPLC analysis are listed as specified identified, specified unidentified and unspecified impurities. Identified impurities, if available, are supported by structural characterization data.
7. Submit a proposed specification that includes a list of tests, reference to analytical procedures, and acceptance criteria. Except for USP listed tests, analytical procedures with supporting validation data should be submitted.
8. Provide a description of the container closure system that will be used to package the drug substance.
9. Provide the stability data for the drug substance according to ICH Q1A(R2) Stability Testing of New Drug Substances and Products to support a proposed expiration dating or retest period.

Drug Product

The methods to be used in, and the facilities and controls used for manufacture, processing, packaging, and holding of the drug product are inadequate to assure its identity, strength, quality, purity, and stability. Specifically, the following information and data must be submitted:

10. Submit the batch formula, including a complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product.

11. Submit a flow chart with detailed description of the manufacturing and packaging process, including in-process controls for the to-be-marketed drug product. In addition, submit an executed master batch record of a representative batch.
12. Submit a proposed specification that includes a list of tests, reference to the analytical procedures, and acceptance criteria. In addition, submit the analytical procedures with supporting validation data.
13. Regarding the _____ syringe:
 - a. Submit a description and clear drawing of the _____ syringe for the market product. Include a description and location of the immediate label.
 - b. To support the qualification of the syringe, submit data for:
 - Physical integrity
 - Compatibility – interaction between the drug product and the syringe
 - _____ studies – _____ syringe and pouch system.
 - c. Submit the source(s) and compositions of the _____ materials, _____ polypropylene (plunger rod), and _____ Grey _____ (plunger stopper). Alternately, provide a reference to the DMF with a letter of authorization (LOA).
14. Regarding the sterilization of the drug product:
 - a. Provide data using the product solution _____ in sterilization validation studies.
 - b. Provide data to confirm the container/closure integrity. Two examples of tests that have been employed for this assessment are the microbial ingress test (using a motile organism) or the dye ingress test.
 - c. This product is administered by injection into the anterior eye chamber. _____ requires that these products meet pharmacopeial requirements for _____. An _____ specification for the finished product should be established.
 - d. _____
 - e. Provide the name and address of the facility where the drug product is sterilized. Include the name of the contact person, telephone and facsimile numbers.
15. Regarding the stability data for the drug product:
 - a. On page 7 of 21, in the paragraph on stability, and in Appendix B5 and B6 (original October 24, 2003 submission), clarify the conditions and testing time for the _____ study.
 - b. Since _____ assay methods are not specific, propose a stability-indicating method, e.g., HPLC, to assay the trypan blue and related impurities.
 - c. Provide stability data performed according to ICH Q1A(R2) Stability Testing of New Drug Substances and Products to support the proposed expiry.
16. Submit a stability protocol that describes the testing periods and conditions, expiration dating, and a post-approval commitment. Stability testing of NDA and future drug product batches should be performed according to the stability protocol.

17. Inspection of the manufacturing facilities for this application are in progress. All facilities must be in compliance with current good manufacturing practice (cGMP) regulations as described in 21 CFR 210 and 211.

We will continue to work with you to reach agreement on acceptable labeling for the application.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level:

1. Describe in detail any significant changes or findings in the safety profile.
2. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
3. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
4. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products to discuss what steps need to be taken before the application may be approved.

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The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2040.

Sincerely,

{See appended electronic signature page}

Jonca C. Bull, M.D.

Director

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

Jonca Bull

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