CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-716

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-716

Prima Pharm, Inc.
Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, California 92121

Dear Mr. Dziabo:

Please refer to your new drug application (NDA) dated October 17, 2003, received October 20, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydase (hyaluronidase injection).

We acknowledge receipt of your submissions dated October 27, December 16, 2003, January 22, and March 8, 17 and 25, 2004.

We also acknowledge receipt of your submission dated April 8, 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 satisfactory responses to the following issues:

Clinical

1. The application does not contain an assessment of the potential to cause allergenicity. A clinical trial that establishes the level of allergenicity of this product should be conducted. This can be established by studying a representative population of patients using a skin test by means of an intradermal injection to determine if the level of allergenicity is less than 10%.

Drug Substance

2. Inspections of the manufacturing facilities for this application have been performed and deficiencies have been conveyed to you. All facilities must in compliance with current good manufacturing practice (cGMP) regulations as described in 21 CFR 210 and 211 prior to approval of this drug product.

3. Provide the following information regarding characterization:
   a. In Appendix 1, sub-sections G, H and I, the hyaluronidase protein band for the USP reference standard and for the Hydase drug product is assigned to band [redacted] while the same assignment for [redacted] and PrimaPharm drug substances is to band [redacted] Please explain this difference in assignments. In addition, conduct and report the results of a hyaluronidase-specific SDS-PAGE experiment to determine the protein band(s) containing the hyaluronidase activity.
   b. Identify and quantify the component(s) of the non-protein portion of the drug substance.
   c. Appendix 1, sub-section K, first page contains a discrepancy between the amount of protein applied to the SDS-PAGE [redacted] and the total protein ([redacted] for the USP standard reference sample. Please clarify.

4. These comments pertain to the drug substance manufactured at [redacted]
   a. Provide [redacted] acceptance criteria and tests for the bovine testes [redacted]
   b. [redacted] should either use a dedicated facility for the manufacturing of hyaluronidase drug substance or provide an adequate, validated equipment and manufacturing area cleaning protocol to ensure no cross contamination from other products.
   c. For the bovine testes obtained from [redacted]
      - [redacted]
      - [redacted]

5. These comments pertain to the drug substance manufacturing process at Prima Pharm:
   a. Provide data on the amounts of starting material, intermediate and final yield. Alternatively, provide a representative executed manufacturing batch record for the drug substance.
   b. A Certificate of Analysis (COA) or release data of a representative batch from Prima Pharm should be provided.

6. Submit the revised specification sheet and stability protocol to reflect these changes to the drug substance:
   a. Establish acceptance criterion and analytical procedure for pH.
   b. Include acceptance criteria and analytical procedures for total protein, hyaluronidase content (mg/mg of protein), protein and non-protein impurities.

7. In the amendment dated March 26, 2004, the contract laboratory of [redacted] was identified to perform [redacted] testing. Provide the name of a contact person, address, telephone and facsimile numbers and CFN for the [redacted]

8. These comments refer to the viral clearance studies:
   a. Viral clearance information was provided for the [redacted] step of the manufacturing process. Typically more than [redacted] step is evaluated to determine an overall level of viral elimination/inactivation. This manufacturing process has other steps that may contribute to the overall viral clearance. Results should be submitted from viral clearance studies performed on at least [redacted] step in your manufacturing process considered to be effective in inactivating/removing viruses.

b. A description of the scale-down process used to perform the viral clearance of the ——— step should be submitted. This description should include the type of [redacted]

c. The results you reported for the viral clearance study for the ——— were derived from a single test. Demonstration of an effective virus removal step should be performed using at least two independent studies.

Drug Product

9. These comments pertain to the drug product manufacturing process:
   a. Revise the master manufacturing batch record and the formulation table to reflect the change in overage from ———.
   b. Submit the release data of a batch manufactured with — overage.
   c. State the size of the commercial production batches.

10. These comments pertain to the container closure system:
   a. Submit data to support the compatibility of the drug product with the container closure system to ensure that the solution is free of leachables and no loss of the drug substance is observed due to absorption to the components.
   b. Provide data to support the compatibility of the drug product with all the other components of the delivery system.

11. Revise the specification sheet and the stability protocol to reflect these changes to the drug product:
   a. [redacted]
   b.
   c. [redacted]

12. Include the validation of any added analytical procedures methods for the drug substance and the drug product and revise the method validation package accordingly.

13. Provide the location of manufacturing equipment within the manufacturing facility and diagrams of product/personnel/component flow through the aseptic processing area.

14 [redacted]

15. Provide pre- and post-filtration holding times for the drug product.

16. Provide depyrogenation and sterilization validation data for the container/closure components and manufacturing equipment.

17. Provide the following information regarding media fills:

a
b
c
d.
e.
f.
g.
h.
i.

18.

19. With regard to the environmental monitoring protocol:

a.
b.
c.
d

20. Provide the stability testing schedule for maintenance of sterility testing and endotoxin testing.

21. Submit the results of the photostability studies for the drug substance and the drug product according to the proposed protocols.

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

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

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 the 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, HFD-550, to discuss what steps need to be taken before the application may be approved.

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

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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