VII. February 16, 2001 complete response letter and subsequent actions

Complete Response Letter: February 16, 2001

Our STN: BL 103951/0

George Morstyn, Ph.D.
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Dr. Morstyn:

This letter is in regard to your biologics license application for darbepoetin alfa submitted under section 351 of the Public Health Service Act. Reference is also made to our teleconference dated September 19, 2000, between representatives of Amgen and CBER, and your response dated October 2, 2000. Reference is also made to our December 15, 2000 Discipline Review letter.

The Center for Biologics Evaluation and Research (CBER) has completed the review of this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Chemistry, Manufacturing, and Controls Section:

1. The [redacted] presented in the BLA for [redacted] of darbepoetin alfa drug product and [redacted] of bulk drug showed a range of [redacted] of the [redacted] Moreover, the method validation for the *in*

[redacted]

[redacted]

Please submit all data supporting your proposed specifications.

2. Regarding drug substance testing and specifications

   a. In accordance with the International Conference on Harmonization document Q6B entitled, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (available at http://www.ifpma.org/ich5q.html), please institute a lot release specification for [redacted] manufacture, and submit data supporting your proposed specification.

   b. As described in your October 2, 2000 submission, the specification for the SDS-PAGE [redacted]

c. Please institute specifications for the relative intensities of the bands observed [redacted] and submit data supporting your proposed specification in your response.

d. Please develop a lot release specification for the minor [redacted] darbepoetin alfa and submit data supporting your proposed specification in your response.

e. Please define the phrase "Conforms to Standard" (CTS), in regard to the [redacted] specification.

f. Please revise the Certificate of Analysis (COA) for bulk drug substance to be in accordance with the above changes, and submit a copy of the revised COA.

3. Regarding immunogenicity of the drug product:

a. The current assay for antibodies to darbepoetin alfa is not sufficiently sensitive. [redacted]

improved quantitative ability. Prior to using the new assay, we request you submit the validation data to your IND for review.

b. We request that you use this assay to re-test archived serum samples from patients in the clinical trials. Please submit the results and revised draft labeling.

c. You submitted information on immunogenicity of darbepoetin alfa in a formulation containing albumin but not the polysorbate-containing, albumin-free formulation. Please provide information on the immunogenicity of the polysorbate formulation of darbepoetin alfa using the new assay. Please submit revised draft labeling.

d. In the event the new assay detects antibodies to either formulation of darbepoetin alfa. [redacted] darbepoetin alfa a[redacted]

Steps to address the above issues should be initiated now, but may be completed with postmarketing commitments. Please describe your plans to address each of these four issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- a proposed schedule for developing and validating each assay and submitting the results to CBER;
- a description of each study, including numbers of serum samples to be tested; and,
- a schedule for conducting each study and submitting of the final study report and applicable revised labeling to the CBER.

4. Please submit validation summaries from three consecutive, successful sterilization runs for all equipment used for the aseptic filling and support operations for the formulation and filling of darbepoetin alfa. These summaries should include, but not be limited to, the following information:

5. Please submit a narrative description of the viable and non-viable environmental monitoring program for class 100 environmentally classified areas at both the Thousand Oaks, California and Juncos, Puerto Rico locations. The information should include the frequency of environmental monitoring; locations monitored; alert and action levels; descriptions of actions taken when alert and action levels are exceeded; and, information on the monitoring program for yeasts and molds.

6. Please provide validation summaries of testing performed supporting product compatibility and microbial retention for the sterilizing [redacted] used in the [redacted] stage at the Juncos, Puerto Rico location.

Clinical Section:

7. Preliminary comments regarding our review of the clinical section of your application were communicated in our Discipline Review letter dated December 15, 2000. In preparing your complete response, please ensure you completely address each deficiency delineated in our December 15, 2000 letter. We acknowledge receipt of your December 28, 2000, submission. You may cross reference applicable sections of that amendment in your complete response to this letter and those sections will be reviewed as part of your complete response.

8. As noted in our Discipline Review letter dated December 15, 2000, the darbepoetin alfa safety database raises concern regarding enhanced susceptibility of patients of African descent to darbepoetin alfa induced hypertension. As described in that letter, we request that you conduct a postmarketing study to further evaluate the risk of hypertension in subjects of African descent. We also requested additional pediatric studies. Please describe your plans to address these issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

   - A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

   - Proposed schedule for conducting the study, including all major milestones for the study (e.g., submission of finalized protocol to the FDA, completion of patient accrual, completion of the study, and submission of the final study report, SAS dataset and applicable revised labeling to the FDA).

   Please be advised that submission of complete protocols for review and comment should be submitted to your IND and may be cross-referenced in your response to this letter.

9. As discussed during the telephone conversation of February 2, 2001, between Ms. Cheryl Anderson and Ms. Nancy Picarello of Amgen, and Dr. Ellis Unger of this office, we understand that you are planning to revise reported rates of adverse events for incorporation in the package insert. Please submit a revised table of adverse events for the proposed package insert, including all events with an incidence of 5% or greater in darbepoetin alfa-treated subjects.

10. Darbepoetin alfa, like other products in this class, is likely to be self-administered by some patients. Therefore, please submit a draft patient information sheet for the product. We request that this label provide information, in a question and answer format, about risks as well as steps for preparation and administration.

We have considered your proposed trade name in consultation with CBER's Advertising and Promotional Labeling Branch and have no objection to your proposed trade name "ARANESP" at this time. However, a formal acceptance of your proposed trade name cannot be given at this time, since another product with a similar name (e.g., sound-alike or look-alike) could be approved prior to the approval of your product.

We reserve comment on the proposed labeling until the application is otherwise acceptable.

You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products – February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Jeanne Delasko, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,

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