



May 9, 2003

CBER-03-011

WARNING LETTER

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

David Bengston  
Vice President Colorado Operations  
Amgen, Inc.  
4000 Nelson Road  
Longmont, Colorado 80503

Dear Mr. Bengston:

The Food and Drug Administration (FDA) has completed its review of the inspection conducted between January 7 and January 24, 2003, of your pharmaceutical manufacturing facility located at 5550 Airport Road, Boulder, Colorado. The inspection revealed significant deviations from current good manufacturing practice (CGMP) in the manufacture of bulk recombinant methionyl human interleukin-1 receptor antagonist (IL-1ra). These violations of the CGMPs render the product adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The inspection also revealed your export of the product in violation of section 801(e)(1) of the FD&C Act, and your failure to notify FDA prior to your implementation of production process changes as required by Title 21, Code of Federal Regulations (CFR), Subchapter F, Parts 600-680, [21CFR 601.12].

Significant deviations observed during the inspection include but are not limited to:

INVESTIGATION OF FAILURES

1. There is no indication that you fully investigated failures or that you extended failure investigations to other batches as appropriate. For example:
  - a. Investigation Report ACOINV-45 documented the presence of [REDACTED] stainless steel particulates in the filter housing of chromatography skids

and in the column resin beds used for the purification of lots 25C008257, 25C008258, and 25C008260. Although the report states that the process itself incorporates numerous steps that remove non-soluble particulates, and that no particulates were present in the filtered purified bulk, a thorough investigation was not conducted or extended to all lots manufactured during the time of the noted discrepancy.

- b. Investigation Report ACOINV-17 documented the presence of [REDACTED] series stainless steel particulates in the membranes of the [REDACTED] skids used for the purification of lots 25027 and 25028. A thorough investigation was not conducted to demonstrate that all lots manufactured during the time of the discrepancy were evaluated.
- c. Investigation Report ACOINV-45 states that the [REDACTED] stainless steel particulates were derived from the construction activities of the [REDACTED] project. However, a thorough investigation was not conducted to demonstrate that the particulates were solely derived from the [REDACTED] project and not derived from a previously identified pump failure or from a combination of the [REDACTED] project and pump failure.
- d. Investigation Report ACOINV-45 states a comprehensive engineering project was executed to flush all process and utility pipes and to replace the gaskets and diaphragms that contained particulates, however, a thorough investigation was not conducted to demonstrate the successful removal of the particulates from all process pipes and support systems.

#### PRODUCTION AND PROCESS CONTROLS

2. Construction of the [REDACTED] and expansion of the support systems, which included making modifications to existing product process pipes, was conducted without adequate change control. There was no protocol describing the tests to be conducted or the data to be collected to ensure the new and existing pipes were clean and suitable for use. Furthermore, there was no documented review of data regarding the cleanliness and suitability of the new pipes.
3. [REDACTED] were installed on each of the inlet and load lines for the chromatography skids and a [REDACTED] filter was installed at the pump outlet for column [REDACTED] without conducting appropriate validation studies.

#### CHANGES TO BE REPORTED

4. You failed to notify FDA's Director, Center for Biologics Evaluation and Research (CBER) of changes to the production process and distributed product made using the change without demonstrating through appropriate validation that the change did not adversely affect the safety and effectiveness of the product. These changes meet the standard for reporting under 21 CFR 601.12. For

example, as stated in Investigation Report, ACOINV-45, as a corrective action, [REDACTED] were installed on each of the inlet and load lines for the chromatography skids and a [REDACTED] was installed at the pump outlet for column [REDACTED] without demonstrating the lack of adverse effect of the changes on the product as they relate to safety or effectiveness, and without notifying the FDA.

#### EXPORT OF PRODUCT

5. You exported products not intended for export in violation of section 801(e) of the FD&C Act. The lots of IL-1ra that did not meet the United States specification for [REDACTED] were not intended for export within the meaning of the Section 801(e)(1) in that the lots intended for export must be identified prior to the start of manufacturing.

We acknowledge receipt of your response dated February 6, 2003, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

##### Item #1 and #2

You explain that Amgen is operating under a “Nonconformance system” which requires a broad level of review for non-conformances with a potential to adversely impact product quality. Please provide a detailed description of the “system.” Your response did not identify steps taken to implement and assure adequate and effective corrective and preventative actions. Additionally, your response did not address steps taken to implement and assure effective change control procedures, including reporting changes to the FDA.

##### Item #3

Please be advised that a product intended for export prior to manufacture will not be deemed adulterated or misbranded provided it complies with section 801(e)(1) of the FD&C Act. The lots of IL-1ra that did not meet the United States specification for [REDACTED] were not intended for export within the meaning of Section 801(e)(1) in that the lots were not identified for export prior to the start of manufacture. Therefore, the export of such lots did not meet all of the requirements for 801(e)’s exemption from the adulteration and misbranding provisions of the FD&C Act. Please state the corrective action you have taken or plan to take to assure that Amgen no longer exports product in violation of section 801(e)(1).

Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facility. It is your responsibility to assure that your operations are in compliance with all requirements of the federal regulations. Federal agencies are advised of the issuance of all Warning

Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action may include license suspension and/or revocation, seizure and/or injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) working days of receipt of this letter of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

Handwritten signature of Mary Malarkey in cursive script, with the initials 'FM' written below the signature.

Scott MacIntire  
Acting Director  
Office of Enforcement

cc: Kevin Sharer  
Chairman / Chief Executive Officer  
Amgen, Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1789