Richard Lit
Director, Regulatory Affairs

AMGEN

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805 447 1000
Direct Dial 805 447.3347
Cellular 805 479 0588
E-mail rlit@amgen com

3249 '04 MAR -8 A9:04

March 5, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, RM 1061
Rockville, MD 20852

Re: Docket No. 2003D-0386
Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

Dear Sir/Madam,

As a global biotechnology company that discovers, develops, manufactures and markets human therapeutics, Amgen is pleased to provide comments regarding the FDA's *Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*. Amgen acknowledges the FDA's effort in the publication of this document in that it will provide additional processes for dialogue leading to resolution of disputes. Our input is intended to further strengthen the document and to clarify the process. General comments follow below; comments on specific text are provided in the attachment.

Comment #1:
Scope of the Guidance

The guidance specifically excludes its applicability for disputes that arise during preapproval inspections (PAI) for human biological drug products. The purpose for this exclusion is not explained. For consistency, this guidance should also apply to PAI for human biological products now regulated by the new Biological Product Offices (Office of Drug Evaluation VI and Office of Biotechnology Products) within CDER.

Comment #2:
Agency Actions during Evaluation/Review Period

It is unclear as to actions the Agency may take while a request for formal dispute resolution is pending. For example, there is no mention that the Establishment Inspection Report will be withheld until the issue is resolved. This should be clarified in the guidance.

2003D-0386 CS

Additionally, any regulatory action regarding an inspection for which the manufacturer has disputed observation(s) should be suspended until the Office of Regulatory Affairs (ORA) has made a determination on the disputed observations(s). In the case of PAIs, where PDUFA timelines require Agency action on the subject application in less then 40 days from the issuance of the 483, the timeline for ORA review of the disputed observation should be shortened accordingly. Any circumstances that would result in the Agency taking a regulatory action while the dispute resolution process is underway should be clarified.

Comment #3:
Issues Not Resolved during an Inspection

Where Agency procedures or practices disallow the manufacturer to discuss scientific or technical issues with FDA management, program officials, inspectors or reviewers who are not physically located at the manufacturer's facility, some processes defined in this guidance may be unduly denied. Such a situation may arise when the investigator or reviewer on site consults with FDA staff in private teleconferences or by other communication devices. These offsite staff may in fact become part of the inspection team, however, the manufacturer does not have the opportunity to resolve issues during the inspection as described in the guidance. When (if) Agency procedures deny the manufacturer the opportunity to resolve scientific or technical issues directly with the consulting FDA management or program officials, undue burden may be placed on the manufacturer and the Agency by requiring that these issues be resolved using the formal processes defined in this guidance.

Additionally, there may be situations during an inspection when a manufacturer may not raise or discuss observation issues. This may be due to either a lack of understanding of the investigator's concerns, lack of time, or that the environment created during the course of the inspection may not be conducive to discussing controversial issues. As a result, the investigator would not have documented the information in the administrative record, which the guidance states the Agency would base all decisions in the formal dispute resolution process. However, if the manufacturer feels this information is relevant, it should be allowed to present the information in requesting formal dispute resolution.

Comment #4:
Tier-One and Tier-Two Dispute Resolution FDA Involvement

There is no provision for the involvement of the FDA District Office in the tier-one dispute resolution process for human biological drug products. Given the movement of these products to CDER, in cases where the District is involved in inspections, we suggest they also be involved in the dispute resolution process.

Furthermore, to inject greater impartiality into the process, review of the manufacturer's dispute should include FDA staff not previously involved in the disputed observation (i.e. staff other than the investigator who made the

observation or Agency staff who may have been consulted by the investigator during the inspection).

For the Tier-Two process, the composition of the Disposition Resolution (DR) Panel (i.e., "representatives from each of the program centers") is unclear. This should be more specific.

Amgen appreciates the opportunity to comment on this draft guidance. If you require further information, please feel free to contact me at (805) 447-3343 or rlit@amgen.com.

Sincerely,

Rick Lit
Director Regulatory Affairs

Attachment

ATTACHMENT

Line Reference*	Comment
25	**Text:** "As these disputes may involve complex judgments and issues that are scientifically important, it is critical to have procedures in place that will encourage open, prompt discussion of disputes and lead to their resolution." **Comment/Rationale:** Add "or technologically based" after "...scientifically important" for clarification.
152	**Text:** "The ORA unit will issue a written response to the manufacturer within 30 days of receipt of the request, noting its agreement with the manufacturer and resolution of the dispute. The resolution may take the form of a letter. It may also take the form of an addendum to the existing Form FDA 483." **Comment:** It should be specifically stated that the resolution would be documented in an addendum to the 483. **Rationale:** If there is no addendum to the 483, the disputed item will be in the historical inspection record and could be subject to follow up in future inspections. This would result in additional disputes.
205	**Text:** "If the DR Panel agrees with the manufacturer on the issue, • The executive secretary of the DR Panel will issue a written response to the manufacturer within 30 days of the meeting, noting its agreement with the manufacturer and resolution of the dispute." **Comment/Rationale:** The form of the resolution (e.g., an addendum to the 483) is not specified. The form of resolution should be consistent with the Tier-One process.

**Guidance used for line references can be located at:*
http://www.fda.gov/OHRMS/DOCKETS/98fr/5804dft.pdf