Guidance for Industry

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 180 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

Copies of this draft guidance document are available on the Internet at http://www.fda.gov/cder/gmp/index.htm. For questions regarding this draft document contact Mary Jane Mathews (301) 594-2847.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Pharmaceutical CGMPs
August 2003

Guidance for Industry

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

Additional copies of this Guidance are available from

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
5600 Fishers Lane, Rockville, MD 20857
Phone 301-827-4573
Internet: http://www.fda.gov/cder/guidance/index.htm.

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
1401 Rockville Pike, Rockville, MD 20852-1448
Phone 800-835-4709 or 301-827-1800
Internet: http://www.fda.gov/cber/guidelines.htm

or

Communications Staff, HFV-12
Center for Veterinary Medicine
7519 Standish Place,
Rockville, MD 20855
Phone 301-827-3800
Internet: http://www.fda.gov/cvm/guidance/published.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Pharmaceutical CGMPs
August 2003

TABLE OF CONTENTS

Draft Guidance For Industry[1]

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document is intended to provide guidance to manufacturers of veterinary and human drugs, including human biological drug products, on how to resolve disputes of scientific and technical issues relating to current good manufacturing practice (CGMP) requirements. Disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements or during the Agency's assessment of corrective actions undertaken as a result of such inspections. 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. This guidance describes procedures for raising such disputes to the Office of Regulatory Affairs (ORA) and center levels and for requesting review by the Dispute Resolution Panel for Scientific and Technical Issues Related to Pharmaceutical CGMP (DR Panel).

Manufacturers may seek clarification of scientific or technical issues with the inspection team at any time during an inspection. Although there are existing processes to encourage dialogue between FDA and manufacturers, the processes described in this document apply to CGMP questions raised during inspections and are intended to supplement the dispute resolution processes currently in place, including:

[1] This guidance has been prepared by the Dispute Resolution Working Group formed as part of the August 2002 FDA Initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach. The Working Group included representatives from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA).

- 21 CFR 10.75, Internal Agency Review of Decisions. Allows manufacturers to ask for a review of Agency decisions at each successive supervisory level through the chain of command, ending with the FDA Commissioner's office.

- CDER/CBER guidance entitled *Formal Dispute Resolution: Appeals Above the Division Level*. Describes procedures a sponsor may use to formally appeal disputes to the office or center level on scientific and procedural issues that arise during drug development, new drug review, and post-marketing oversight processes. The guidance may be found on CDER and CBER's Web sites[2].

- CVM draft guidance entitled *Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine (CVM),* May 2003. Describes procedures for handling requests for internal review of scientific controversies relating to decisions affecting animal drugs or other products that are regulated by CVM. The guidance may be found on CVM's Web site.[3]

- Investigations Operations Manual (IOM), Chapter 5, Subchapter 510, Sections 512 (Report of Observations) and 516 (Discussions with Management). Describes processes for discussing inspectional observations with a manufacturer. The IOM is available on ORA's Web site.[4]

For the purposes of this document, the term *manufacturer*[5] includes any domestic or foreign applicant or manufacturer of a human or veterinary drug, or human biological drug product regulated by the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) or section 351 of the Public Health Service Act (the PHS Act).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE OF THE GUIDANCE

The policies and procedures described in this guidance document cover all disputes on scientific or technical issues related to CGMP that arise as the result of CGMP and preapproval inspections (PAI) for manufacturers of veterinary and human drug products and CGMP inspections for human biological drug products. For disputes that arise during prelicense and

[2] The CDER/CBER guidance can be found on the Internet at http://www.fda.gov/cder/guidance/index.htm *and* http://www.fda.gov/cber/gdlns/dispute.htm.

[3] The CVM guidance can be found on the Internet at: http://www.fda.gov/cvm/index/updates/disputegl.htm.

[4] The IOM can be found on the Internet at: http://www.fda.gov/ora/inspect_ref/iom/iomtc.html.

[5] The activities of a manufacturer encompass the processes and functions described in 21 CFR 207.3(8), 21 CFR 210.3(12), and 21 CFR 600.3(t).

preapproval inspections for human biological drug products or for application review issues that arise during PAI inspections for human or veterinary drug products, the existing CDER/CBER and CVM guidances listed in Section I of this document should continue to be used.

This guidance does not cover disputes over procedures or administrative matters that may arise during the inspection process. At any time, a manufacturer may informally raise a procedural or administrative matter with ORA or with the CDER, CBER or CVM Ombudsman. The procedures described in this guidance do not apply to such informal dispute resolution through the CDER, CBER or CVM Ombudsman.

III. DISPUTE RESOLUTION PROCESS

During inspections of manufacturers, investigators are encouraged to discuss observations relating to manufacturing quality as they are observed, or on a daily basis to minimize surprise, errors, and misunderstandings when a Form FDA 483 is issued. At the conclusion of an inspection, investigators usually meet with the manufacturer's management to again discuss observations and solicit views and additional relevant information. These processes are described in detail in the Investigations Operations Manual (IOM), Sections 512 and 516, as listed in Section I of this document.

When a scientific or technical issue arises during an inspection, we recommend that a manufacturer initially attempt to reach agreement on the issue informally with the investigator. A manufacturer should discuss with the investigator any observation that the manufacturer believes is not justified from a scientific or technical standpoint. As appropriate, the investigator can consult with FDA management or program officials, or appropriate product or technical experts. If agreement on the issue is not reached with the investigator prior to issuance of the Form FDA 483, a manufacturer can formally request dispute resolution after the investigator issues the Form FDA 483.

Certain scientific or technical issues may be too complex or time-consuming to resolve during the inspection. If resolution of a scientific or technical issue is not accomplished through informal mechanisms prior to the issuance of a Form FDA 483, manufacturers can use the formal two-tiered dispute resolution process described in this guidance.

- Tier one of the formal dispute resolution process refers to scientific or technical issues raised to the ORA and center levels.
- Tier two of the formal dispute resolution process refers to scientific or technical issues raised to the DR Panel.

These processes are described in detail in the following subsections.

A. Tier-One Dispute Resolution at the Office of Regulatory Affairs and Center Levels

Pharmaceutical manufacturers can formally dispute the scientific or technical basis for CGMP inspectional observations after issuance of a Form FDA 483. In such cases, the formal dispute resolution process starts in the appropriate ORA unit[6] as listed below and may advance to the applicable center.

- For domestic manufacturers of veterinary and human drugs, the formal dispute resolution process begins in the appropriate district office, ORA.

- For foreign manufacturers of veterinary and human drugs, the formal dispute resolution process begins in the Division of Field Investigations, ORA.

- For domestic or foreign manufacturers of human biological drug products inspected by Team Biologics, the formal dispute resolution process begins in the Office of Enforcement, ORA.

A manufacturer should seek clarification of a disputed scientific or technical issue within 10 business days of the completion of an inspection. FDA may refuse to address a dispute resolution request not raised during this time frame.

If a manufacturer disagrees with the scientific or technical basis for an observation listed by an investigator on a Form FDA 483, the following steps would be taken:

1. The manufacturer can file a written request for formal dispute resolution with the appropriate ORA unit as listed above. The manufacturer should provide all supporting documentation and arguments for review.

2. The appropriate ORA unit will evaluate the written request for formal dispute resolution.

If the ORA unit agrees with the manufacturer,

- 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.

- All disputes resolved at the ORA level will be copied to the relevant program center for information and public dissemination.

[6] For the purposes of Sections III A and B in this document, the phrase *ORA unit* will refer to the district office, the Division of Field Investigations, or the Office of Enforcement, as appropriate.

If the ORA unit disagrees with the manufacturer,

- The ORA unit will issue a written response to the manufacturer generally within 30 days of receipt of the request. Responses that disagree with a manufacturer's position will incorporate a review and decision by the relevant program center, which may require additional time as described below.

- The written response will be copied to the relevant program center for information and public dissemination after appropriate redaction, in accordance with applicable requirements.

If the ORA unit is unable to complete its review of the request and respond within 30 days, the ORA unit will notify the manufacturer, explain the reason for the delay (which may include the need for an additional 30 days for center review), and discuss the time frame for completing the review.

3. If a manufacturer disagrees with the tier-one decision, the manufacturer can appeal that decision to the DR Panel.

B. Tier-Two Dispute Resolution with the DR Panel on Scientific and Technical Issues

The DR Panel provides a formal way for manufacturers to defend the science in their manufacturing and quality control processes before a neutral panel of experts and to appeal an ORA and center level decision concerning the science underlying the inspectional observation.

The DR Panel resides at the Agency level. The DR Panel considers requests for tier-two dispute resolution by manufacturers and provides an opportunity for a manufacturer to present its case in support of its position on a scientific or technical issue. The DR Panel's membership includes representatives from each of the program centers, but will not include decision makers who have addressed the disputed issue at the ORA and center level.

If a manufacturer disagrees with the tier-one decision in the formal dispute resolution process, the manufacturer can file a written request for formal dispute resolution by the DR Panel. The manufacturer should provide the written request for formal dispute resolution and all supporting documentation and arguments to the DR Panel for review within 60 days of receipt of the tier-one decision.

The DR Panel will evaluate the written request for formal dispute resolution. The DR Panel will determine whether or not to consider the specific issue in the appeal. If necessary, additional experts may be added to the DR Panel to facilitate evaluation of the specific issue.

If the DR Panel determines that the request is appropriate for review, it will bring the issue to the next scheduled DR Panel meeting for which there is time available on the agenda.

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.

- All disputes resolved at the DR Panel level will be copied to the relevant FDA units for their information and public dissemination after appropriate redaction, in accordance with applicable requirements.

If the DR Panel disagrees 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 decision on the issue, except as provided below.

- The executive secretary of the DR Panel will notify the relevant FDA units for their information and public dissemination after appropriate redaction, in accordance with applicable requirements.

If the DR Panel determines that the request does not qualify for review (see Section IV), the executive secretary of the DR Panel will notify the manufacturer in writing within 30 days of receipt of the appeal and communicate the DR Panel's decision to the program offices.

If FDA is unable to complete its review of the request and respond within 30 days, the executive secretary of the DR Panel will notify the manufacturer, explain the reasons for the delay, and discuss the time frame for completing the review.

C. How to Request Formal Dispute Resolution

All Agency decisions in the formal dispute resolution process will be based on the manufacturer's administrative record that was available at the time of the inspection, unless a manufacturer can provide a reasonable explanation why it was unable to present relevant information during the inspection. No new information should be submitted as part of a request for formal dispute resolution. If a manufacturer presents new information about an issue in requesting formal dispute resolution, the matter will be returned to the ORA unit for review as appropriate.

The Agency may take a regulatory action under appropriate circumstances while a request for formal dispute resolution is pending.

The following list of addresses can be used to request formal dispute resolution.

1. For a tier-one dispute resolution request from domestic manufacturers of veterinary and human drugs, the request should be submitted to:

Director of the district office responsible for the inspection
The following Internet site lists district office addresses:
http://www.fda.gov/ora/inspect_ref/iom/iomoradir.html.

2. For a tier-one dispute resolution request from foreign manufacturers of veterinary and human drugs, the request should be submitted to:

Director, Division of Field Investigations
Office of Regional Operations
Office of Regulatory Affairs
Food and Drug Administration
Mail Code: HFC-100
5600 Fishers Lane, Room 13-64
Rockville, Maryland 20857

3. For a tier-one dispute resolution request from domestic or foreign manufacturers of human biological drug products inspected by Team Biologics, the request should be submitted to:

Director, Division of Compliance Management and Operations
Office of Enforcement
Office of Regulatory Affairs
Food and Drug Administration
Mail Code: HFC-210
5600 Fishers Lane
Rockville, MD 20857

4. For a tier-two dispute resolution request, the request should be submitted to the appropriate center contact as listed below:

- For CDER:

Formal Dispute Resolution Project Manager (DPRM)
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Mail Code: HFD-320
5600 Fishers Lane
Rockville, MD 20857

- For CVM:

Ombudsman
Office of the Center Director
Center for Veterinary Medicine

Food and Drug Administration
Mail Code: HFV-7
7519 Standish Place
Rockville, MD 20855

- For CBER:

Assistant to the Director for Policy
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
Mail Code: HFM-600
1401 Rockville Pike, Suite 200N
Rockville, MD 20852

D. Supporting Information to be Provided by Manufacturers

All requests for formal dispute resolution should be in writing and include adequate information to explain the nature of the dispute and to allow the Agency to act quickly and efficiently. Each request should include the following:

1. Cover sheet that clearly identifies the submission in bold, uppercase letters:

   REQUEST FOR TIER-ONE DISPUTE RESOLUTION

   or

   REQUEST FOR TIER-TWO DISPUTE RESOLUTION (REVIEW BY THE DISPUTE RESOLUTION PANEL FOR SCIENTIFIC AND TECHNICAL ISSUES RELATED TO PHARMACEUTICAL CGMP)

2. Name and address of manufacturer inspected (as listed on the Form FDA 483)

3. Date of inspection (as listed on the Form FDA 483)

4. Date the Form FDA 483 issued (from the Form FDA 483)

5. FEI Number, if available (from the Form FDA 483)

6. Names and titles of FDA employees who conducted inspection (from the Form FDA 483)

7. Office responsible for the inspection, e.g., district office, as listed on the Form FDA 483

8. Application number if the inspection was a preapproval inspection

9. Comprehensive statement of each issue to be resolved

   - Identify the observation in dispute.
   - Clearly present the manufacturer's scientific position or rationale concerning the issue under dispute with any supporting data.
   - State the steps that have been taken to resolve the dispute, including any informal dispute resolution that may have occurred before the issuance of the Form FDA 483.
   - Identify possible solutions.
   - State expected outcome.

10. Name, title, telephone and fax number, and e-mail address (as available) of manufacturer contact.

E. FDA Response to Requests for Dispute Resolution

FDA will respond in writing to all requests for dispute resolution filed under the procedures described in this guidance. The written response should specifically agree or disagree with the outcome desired by the manufacturer, agree or disagree with parts of the proposed outcome, or indicate a resolution that is different from that proposed by the manufacturer. If the Agency does not agree with the manufacturer's position, the response should include reasons for the disagreement.

The Agency official responsible for replying to a request for dispute resolution should make all reasonable efforts to resolve the dispute and provide a written response to the manufacturer according to timelines suggested above in Section III. A and B.

IV. SUITABILITY OF ISSUES FOR FORMAL DISPUTE RESOLUTION

Any dispute involving a scientific or technical issue related to CGMP regulations that arises during an FDA inspection, as discussed above, may be suitable for the dispute resolution process described in this guidance.

The following text provides examples concerning the appropriateness of several issues for the dispute resolution process detailed in this guidance.

A. Failure to Comply With a Precise Element of CGMP Regulations

According to 21 CFR 211.100(a), a manufacturer producing a finished pharmaceutical product must have written procedures for production and process controls, and these written procedures must be designed to ensure that the drug has the identity, strength, quality, and purity it purports or is represented to have.

- Failure to have written procedures for production and process controls would be a failure to comply with a precise element of the CGMP regulations and would not be appropriate for the formal dispute resolution process described in this document.

- However, observations pertaining to the adequacy of the process and production control design activities could be subject to scientific debate and may be appropriate for dispute resolution as described in this guidance.

Another example relates to the regulatory provisions governing the testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84), which require appropriate sampling, testing, or examination of each lot of components, drug product containers, or closures.

- Failure to conduct testing or examination of each lot would be failure to comply with a precise element of the regulations and would not be appropriate for the formal dispute resolution process described in this guidance.

- However, the appropriateness of a particular test or sampling scheme could involve the exercise of scientific judgment. A disagreement between a manufacturer and an investigator concerning the adequacy of a particular test or sampling scheme could be subject to scientific debate and may be appropriate for dispute resolution as described in this guidance.

A third example relates to the CGMP regulation requirements that a manufacturer thoroughly investigate any unexplained discrepancy associated with its review of product production and control records (21 CFR 211.192).

- Failure to investigate an unexplained discrepancy would be a failure to comply with a precise element of the CGMP regulations and would not be appropriate for the formal dispute resolution process described in this guidance.

- However, the extent or adequacy of the investigation could be subject to scientific debate. Observations pertaining to the adequacy of an investigation into an unexplained discrepancy may also be appropriate for dispute resolution as described in this guidance.

B. Failure to Comply With a Precise Requirement Established in an Approved Application

If, as part of the conditions established in an approved application, a manufacturer is required to conduct a particular test on a finished product and the manufacturer fails to conduct that test, this failure represents a failure to comply with a precise requirement established in an approved application. Any disagreement about the need for such a test should be raised in the application review process, is not appropriate for the dispute resolution process described in this guidance,

and should be raised using the processes described in the CDER/CBER and CVM guidances listed in Section I of this document.

C. The Regulatory Significance of Failing to Comply With a Precise Requirement

The CGMP regulations require that all changes to production and process control procedures be approved by the quality control unit (21 CFR 211.100(a)). If a manufacturer makes a change in production and process control procedures, but does not obtain approval of those procedures by the manufacturer's quality control unit, this would be a failure to comply with a precise requirement of the CGMP regulations. The manufacturer may contend that the failure in this particular case was not significant because it did not have an adverse effect on product quality and may convey this contention to the Agency through existing informal communication channels, including Form FDA 483-response correspondence.

In such a case, the significance of this observation would not be appropriate for dispute resolution as described in this guidance, as the observation concerns a failure to comply with a precise requirement of the regulations. The regulatory significance of an observation is determined by the Agency after considering all relevant information, including the manufacturer's response to the inspectional observations. The Agency encourages manufacturers to provide all information relevant to the regulatory significance of an observation as part of this response, but such disputes are not within the scope of this guidance on scientific and technical disputes concerning the interpretation and application of CGMP requirements.

Manufacturers must have internal written production and process control procedures (21 CFR 211.100(a)), and, as part of these procedures, manufacturers often establish procedural *action limits* that are tighter than release specifications. When the *action limits* are exceeded, the internal written procedures may call for some type of investigation to determine if the process is drifting toward a loss of control, or the procedures may call for other assessments to determine if the product will meet appropriate specifications throughout its expected shelf life. If a manufacturer's internal written procedures require certain actions when *action limits* are exceeded, failure to follow these written production and process control procedures is a failure to comply with 21 CFR 211.100(b). The manufacturer may contend that this failure is not significant in that the product met all regulatory specifications when released. As discussed above, this contention about significance is not appropriate for the formal dispute resolution process described in this guidance.

D. Issues Not Raised During the Inspection

If, during an inspection, an investigator notes what appears to be an objectionable condition and a manufacturer disagrees with that observation, the manufacturer should voice its disagreement with the investigator. By doing so, the investigator has the opportunity to evaluate the manufacturer's position and consult, as needed, with Agency experts. In some cases, the Agency will not accept a request for dispute resolution concerning a disagreement that was not initially raised by the manufacturer during the inspection. Unless the manufacturer shows it was unable

to raise its disagreement during the inspection, the Agency believes that accepting such a request would discourage open discussion of disagreements between investigators and manufacturers and would hinder the Agency's ability to quickly and informally resolve disputes in an efficient manner.

V. COMMUNICATION OF DISPUTE RESOLUTION DECISIONS

Unless the decisions made in the dispute resolution process involve information that would otherwise be withheld under FDA's regulations and the applicable statutes, FDA believes that decisions reached during the dispute resolution process should be made publicly available on the FDA Web site after appropriate redaction, in accordance with applicable requirements. Information gained from these decisions should promote consistent application and interpretation of drug quality-related regulations. These decisions will be publicly available consistent with FDA's good guidance practices, FDA's disclosure regulations (21 CFR Part 20), and applicable statutes.