

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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[Docket No. FDA-2008-N-0047] (formerly Docket No. 2008N-0005)

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by *[insert date 30 days after date of publication in the Federal Register]*.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-6974, or e-mailed to *baguilar@omb.eop.gov*. All comments should be identified with the OMB control number 0910-0563. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Elizabeth Berbakos, Office of Information Management (HFA-710), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-796-3792.

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SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice—(OMB Control Number 0910–0563)—Extension

The guidance is intended to provide information 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). Disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements, or during FDA's assessment of corrective actions undertaken as a result of such inspections. The guidance provides procedures that encourage open and prompt discussion of disputes and lead to their resolution. The 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 (DR) Panel (the DR Panel).

When a scientific or technical issue arises during an FDA inspection, the manufacturer should initially attempt to reach agreement on the issue informally with the investigator. 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 Form FDA 483, the manufacturer can formally request DR and can use the formal two-tiered DR process described in the guidance.

Tier-one of the formal DR process involves scientific or technical issues raised by a manufacturer to the ORA and center levels. If a manufacturer disagrees with the tier-one decision, tier two of the formal DR process would then be available for appealing that decision to the DR Panel.

The written request for formal DR to the appropriate ORA unit should be made within 30 days of the completion of an inspection, and should include all supporting documentation and arguments for review, as described below. The written request for formal DR to the DR Panel should be made within 60 days of receipt of the tier-one decision, and should include all supporting documentation and arguments, as described in the following paragraphs.

All requests for formal DR should be in writing and include adequate information to explain the nature of the dispute and to allow FDA to act quickly and efficiently. Each request should be sent to the appropriate address listed in the guidance and include the following:

- Cover sheet that clearly identifies the submission as either a request for tier-one DR or a request for tier-two DR;
- Name and address of manufacturer inspected (from Form FDA 483);
- Date of inspection (from Form FDA 483);
- Date the Form FDA 483 issued (from Form FDA 483);
- FEI Number, if available (from Form FDA 483);
- FDA employee names and titles that conducted inspection (from Form FDA 483);
- Office responsible for the inspection, e.g., district office (from Form FDA 483);
- Application number if the inspection was a preapproval inspection;
- 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 DR that may have occurred before the issuance of Form FDA 483;
- Identify possible solutions;
- State expected outcome;
- Name, title, telephone and fax number, and e-mail address (as available) of manufacturer contact.

The guidance was part of the FDA initiative "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach," which was announced in August 2002. The initiative focuses on FDA's current CGMP program and covers the manufacture of veterinary and human drugs, including human biological drug products. The agency formed the Dispute Resolution Working Group comprising representatives from ORA, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Veterinary Medicine (CVM). The working group met weekly on issues related to the DR process and met with stakeholders in December 2002 to seek their input.

The guidance was initiated in response to industry's request for a formal DR process to resolve differences related to scientific and technical issues that arise between investigators and pharmaceutical manufacturers during FDA inspections of foreign and domestic manufacturers. In addition to encouraging manufacturers to use currently available DR processes, the guidance describes the formal two-tiered DR process explained previously in this document. The guidance also covers the following topics:

- The suitability of certain issues for the formal DR process, including examples of some issues with a discussion of their appropriateness for the DR process.

- Instructions on how to submit requests for formal DR and a list of the supporting information that should accompany these requests.

- Public availability of decisions reached during the dispute resolution process to promote consistent application and interpretation of drug quality-related regulations.

Description of Respondents: Pharmaceutical manufacturers of veterinary and human drug products and human biological drug products.

Burden Estimate: Based on the number of requests for tier-one and tier-two DR received by FDA since the guidance published in January 2006, FDA estimates that approximately two manufacturers will submit approximately two requests annually for a tier-one DR, and that there will be one appeal of these requests to the DR Panel (request for tier-two DR). FDA estimates that it will take manufacturers approximately 30 hours to prepare and submit each request for a tier-one DR, and approximately 8 hours to prepare and submit each request for a tier-two DR. Table 1 of this document provides an estimate of the annual reporting burden for requests for tier-one and tier-two DRs.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours Per Response	Total Hours
Requests for Tier-One DR	2	1	2	30	60
Requests for Tier-Two DR	1	1	1	8	8
Total					68

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

In the **Federal Register** of January 22, 2008 (73 FR 3729), FDA published a 60-day notice requesting public comment on the information collection provisions. We received one comment in response to the January 22, 2008,

Federal Register notice. The comment asked 3 questions about the DR process set forth in the guidance.

First, the comment asked how many working days are taken by the ORA and center levels to reach a decision after receipt of a request for tier-one DR.

FDA Response — As explained in Section III.A of the guidance, 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. 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, and 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.

Second, the comment asked how many working days are taken by the DR Panel to reach a decision after receipt of a request for tier-two DR.

FDA Response — As explained in Section III.B of the guidance, if the DR Panel determines that the request is appropriate for review, it will schedule a meeting to discuss the issue within 90 days. 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. 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. If the DR Panel determines that the request does not qualify for review, the executive secretary

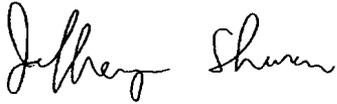
of the DR Panel will notify the manufacturer in writing within 30 days of receipt of the appeal. If FDA is unable to complete its review of the request and respond within 30 days, the executive secretary of the DR Panel will notify the manufacturer, explain the reasons for the delay, and discuss the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

Third, the comment asked whether “the manufacturing facility is approvable or to be re-inspected” if the dispute is not resolved at the end of the tier-two DR stage.

FDA Response — As described in the guidance, it is FDA’s intention to resolve through the DR process all issues raised by the manufacturer. If FDA agrees with the manufacturer, the Form FDA 483 that prompted the request for formal dispute resolution would be revised or rescinded. If FDA disagrees with the manufacturer’s request, the issues raised in the Form FDA 483 stand and FDA would expect compliance with the applicable CGMP requirements, which FDA may verify by re-inspection.

Dated: 7/25/08

July 25, 2008.



Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

[FR Doc. 08-????? Filed ??-??-08; 8:45 am]

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