SUPPORTING STATEMENT

Guidance for Industry - Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

A. Justification

1. Circumstances of Information Collection

This information collection approval request is for a Food and Drug Administration (FDA) guidance for industry entitled "Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP." The guidance was drafted as 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 the Office of Regulatory Affairs (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 dispute resolution 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 dispute resolution 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 dispute resolution processes, the guidance describes a formal two-tiered dispute resolution process that provides a formal mechanism for requesting review and decision on issues that arise during inspections:

- Tier-one of the dispute resolution process provides a mechanism to raise scientific or technical issues to the ORA and center levels.
- Tier-two of the dispute resolution process provides a mechanism to raise scientific or technical issues to the agency's Dispute Resolution Panel for Scientific and Technical Issues Related to Pharmaceutical CGMP (DR Panel).

The guidance also covers the following topics.

- The suitability of certain issues for the formal dispute resolution process, including examples of some issues with a discussion of their appropriateness for the dispute resolution process.
- Instructions on how to submit requests for formal dispute resolution 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.

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 the FDA 483, the manufacturer can formally request dispute resolution and can use the formal two-tiered dispute resolution process described in the draft guidance.

Tier-one of the formal dispute resolution 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 dispute resolution process would then be available for appealing that decision to the DR Panel.

If a manufacturer disagrees with the scientific or technical basis for an observation listed by an investigator on an FDA 483, the manufacturer can file a written request for formal dispute

resolution with the appropriate ORA unit as described in the draft guidance. The request for formal dispute resolution should be made within 10 days of the completion of an inspection, and should include all supporting documentation and arguments for review, as described below. 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, as described below, to the DR Panel within 60 days from issuance of the tier-one decision.

All requests for formal dispute resolution 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 dispute resolution or a request for tier-two dispute resolution;
- Name and address of manufacturer inspected (as listed on FDA 483);
- Date of inspection (as listed on FDA 483);
- Date FDA 483 issued (from FDA 483);
- FEI Number, if available (from FDA 483);

- FDA employee names and titles that conducted inspection (from FDA 483);

- Office responsible for the inspection, e.g., district office, as listed on 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 dispute resolution that may have occurred before the issuance of the FDA 483.
    - Identify possible solutions.
    - State expected outcome.

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

2. Purpose and Use of Information

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 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 will encourage open and

prompt discussion of disputes and lead to their resolution. The guidance describes procedures for raising such disputes to the ORA and center levels and for requesting review by the DR Panel.

3. Use of Improved Information Technology

The guidance requests that the information be submitted in writing and mailed to the appropriate office listed in the guidance.

4. Efforts to Identify Duplication

The information collection requested under the guidance does not duplicate any other information collection.

5. Involvement of Small Entities

Although new drug development is typically an activity completed by large multinational drug firms, the information collection requested under the guidance applies to small as well as large companies. Under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements.

6. Consequences If Information Collected Less Frequently

The frequency of information submission recommended by the guidance is intended to provide assist manufacturers on how to resolve disputes of scientific and technical issues relating to CGMP. The guidance provides procedures that will encourage open and prompt discussion of disputes and lead to their resolution. The guidance describes procedures for raising such disputes to the ORA and center levels and for requesting review by the DR Panel. These benefits will be lessened without the assistance provided by the guidance.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

This guidance contains no inconsistency with the guidelines_ in 5 CFR 1320.5(d)(2).

8. Consultation Outside the Agency

In the Federal Register of September 5, 2003 (68 FR 52777), FDA announced the availability of a draft guidance for industry entitled "Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP," and requested comments for 60 days on the information collection.

In the Federal Register of January 22, 2008 (73 FR 3729), FDA requested comments on this information collection. We received one comment. 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.

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this guidance.

10. Assurance of Confidentiality

Confidentiality of the information submitted under this guidance is protected under 21 CFR 312.130 and 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Based on the number of requests for tier-one and tier-two dispute resolution received by FDA since the guidance published in January 2006, FDA estimates that approximately 2 manufacturers will submit approximately 2 requests annually for a tier-one

dispute resolution, and that there will be 1 appeal of these requests to the DR Panel (request for tier-two dispute resolution). FDA estimates that it will take manufacturers approximately 30 hours to prepare and submit each request for a tier-one dispute resolution, and approximately 8 hours to prepare and submit each request for a tier-two dispute resolution. Table 1 of this document provides an estimate of the annual reporting burden for requests for tier-one and tier-two dispute resolutions.

Estimated Annual Reporting Burden[1]					
	Number of Respondents	**Number of Responses per Respondent**	**Total Annual Responses**	**Hours per Response**	**Total Hours**
Requests for Tier-One Dispute Resolution	2	1	2	30	60
Requests for Tier-Two Dispute Resolution	1	1	1	8	8
Total					**68**

[1]There are no capital costs or operating and maintenance costs associated with this collection.

13. Estimates of Annualized Cost Burden to Respondents

FDA has estimated an average industry wage rate of $50.00 per hour for preparing and submitting the information collection under this guidance. Using the averaged wage rate of $50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is $3,400 (68 x $50).

14. Estimates of Annualized Cost Burden to the Government

FDA estimates that review by FDA staff of the submissions recommended by the guidance would require approximately 10 hours per request.

15. Changes In Burden

The reduced burden is the result of fewer requests than originally anticipated.

16. Time Schedule, Publication, and Analysis Plans

There are no publications.

17. Displaying of OMB Expiration Date

The agency is not seeking to display the expiration date for OMB approval of the information collection.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement

identified in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.

PAPERWORK REDUCTION ACT SUBMISSION

Please read the instructions before completing this form. For additional forms or assistance in completing this form, contact your agency's Paperwork Clearance Officer. Send two copies of this form, the collection instrument to be reviewed, the supporting statement, and any additional documentation to: Office of Information and Regulatory Affairs, Office of Management and Budget, Docket Library, Room 10102, 725 17th Street NW, Washington, DC 20503.

1. Agency/Subagency originating request

FDA

2. OMB control number b. [x] None

a. 0910 – 0563

3. Type of information collection (*check one*)

a. [x] New Collection

b. [ ] Revision of a currently approved collection

c. [ ] Extension of a currently approved collection

d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired

e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired

f. [ ] Existing collection in use without an OMB control number

For b-f, note Item A2 of Supporting Statement instructions

4. Type of review requested (*check one*)

a. [x] Regular submission

b. [ ] Emergency - Approval requested by at close of comment period

c. [ ] Delegated

5. Small entities

Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No

6. Requested expiration date

a. [X] Three years from approval date b. [ ] Other Specify:____/

7. Title Guidance for Industry - Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

8. Agency form number(s) (*if applicable*)

9. Keywords sponsors, drugs. clinical investigation

10. Abstract This guidance provides recommendations to

11. Affected public (*Mark primary with "P" and all others that apply with "x")*

a. ___ Individuals or households d. ___ Farms

b. _x_ Business or other for-profit e. ___ Federal Government

c. ___Not-for-profit institutions f. ___ State, Local or Tribal Government

12. Obligation to respond (*check one*)

a. [x] Voluntary- (guidance document)

b. [ ] Required to obtain or retain benefits

c. [ ] Mandatory

13. Annual recordkeeping and reporting burden

a. Number of respondents 2 _____

b. Total annual responses 3 _____

1. Percentage of these responses collected electronically Varies, based on sponsors voluntarily following the guidances

c. Total annual hours requested 68 _____

d. Current OMB inventory 790 _____

e. Difference _____

f. Explanation of difference

1. Program change _____

2. Adjustment _____

14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)*

a. Total annualized capital/startup costs 0

b. Total annual costs (O&M) 0

c. Total annualized cost requested 0

d. Current OMB inventory 0

e. Difference 0

f. Explanation of difference

1. Program change _____

2. Adjustment _____

15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*)

16. Frequency of recordkeeping or reporting *(check all that apply)*

a. [ ] Recordkeeping b. [ ] Third party disclosure

a. __ Application for benefits e.__ Program planning or management b. __ Program evaluation f.__ Research c. __ General purpose statistics g. x Regulatory or compliance d. __ Audit	c. [x] Reporting 1. [x] On occasion 2. [ ] Weekly 3. [ ] Monthly 4. [ ] Quarterly 5. [ ] Semi-annually 6. [ ] Annually 7. [ ] Biennially 8. [ ] Other (describe) _____
17. Statistical methods Does this information collection employ statistical methods [ ] Yes [x] No	18. Agency Contact (person who can best answer questions regarding the content of this submission) Name: Elizabeth Berbakos Phone: 827-1482

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