

January 30, 2004

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

Re: Docket 2003D-0386; *Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice*

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) *Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice* (Draft Guidance). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than \$30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA applauds FDA's efforts to revamp the current good manufacturing practice (cGMP) requirements generally and to implement a dispute resolution process for cGMP inspections in particular. There is a critical need for a dispute resolution process tailored specifically for the complex scientific and technical issues that arise during cGMP inspections. Pharmaceutical manufacturing facilities increasingly are employing advanced technology and innovative processes to enhance both productivity and quality. As a result, the issues that arise during inspections are becoming increasingly complex and specialized. Often, these issues can not be resolved under existing procedures during the actual inspection and instead require the application of expertise from other parts of the Agency.

Accordingly, PhRMA is pleased that FDA is proposing to implement a dispute resolution process tailored specifically for the cGMP inspection context. Although PhRMA believes the proposal can and should be strengthened (as discussed more fully below), this Draft Guidance is an important first step to implementing an effective and efficient dispute resolution process that meets the needs of both FDA and industry.

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Pharmaceutical Research and Manufacturers of America

PhRMA's complete comments are set forth below.

Tier One Comments

The Ten-Day Time Frame Is Too Short. The Draft Guidance requires manufacturers to submit requests for formal dispute resolution within ten (10) business days of the completion of an inspection. It further states that FDA may refuse to address a dispute resolution request not raised during this time frame. While PhRMA supports the timely resolution of cGMP disputes, we believe this ten day time limit is unduly circumscribed and may preclude manufacturers from taking advantage of the new dispute resolution procedures or result in dispute resolution requests that are incomplete or of lesser quality.

The Draft Guidance requires manufacturers to "provide all supporting documentation and arguments for review" in their Tier I request. Moreover, data and arguments not included in the Tier I request will not be accepted in later stages of review, including Tier II. Since the information and arguments submitted in the initial dispute resolution request form the basis for all subsequent FDA decisions, including the Tier II process, it is critical that manufacturers have sufficient time to ensure that their Tier I request is complete and comprehensive and includes all relevant scientific and technical data. While PhRMA expects that many such requests can and will be prepared within ten days, companies should have the flexibility to take more than ten days when necessary without giving up the right to the formal dispute resolution process. PhRMA thus requests that the time limit for initiating formal dispute resolution be extended to thirty (30) days. PhRMA believes that this will result in better Tier I submissions – and, hence, better Agency decision-making in both Tier I and Tier II – without materially delaying the dispute resolution process.

Finally, to avoid uncertainty over when the thirty day time frame is triggered, PhRMA suggests revising the Draft Guidance to indicate that the time frame begins to run upon issuance of the 483 that contains the observation under dispute.

Firms Must Be Able To Present Their Position To The Relevant Center. The Tier I process contemplates review by the relevant Program Center in situations where the district office disagrees with the manufacturer. While PhRMA supports Center review during the Tier I process, PhRMA believes that manufacturers should have the ability to participate in this stage of the dispute resolution process. As currently drafted, FDA's proposal does not appear to envision any role for the individual firm in this part of the appeal process or enable any communication whatsoever between individual firms and the Program Center decision makers. The proposal instead contemplates that all contact with the relevant program centers will be made by the district office. Individual firms essentially are cut out of this part of the Tier I process and must instead rely on the district decision makers to advocate or clarify the company's position.

PhRMA believes that firms should have the ability to present their own position -- including the scientific and technical information supporting that position -- to the Program Center decision makers. Individual firms should also have the opportunity to respond to the district decision makers and present counter-arguments and/or clarifying information to the Program Center. This is particularly important given the complex scientific and technical issues involved in many such disputes. Without this balance, there is an unacceptable risk that important scientific and/or technical information will not be fully or adequately presented to the Center decision makers and that erroneous observations will be perpetuated.

These risks can be avoided by permitting the manufacturer to communicate directly with the Center decision makers in response to the district's position. Moreover, this can be done without unduly delaying the process by requiring a company response within ten days of receiving the district's adverse decision. In sum, the Tier I process, at a minimum, should be revised to permit full participation by firms in all levels of Agency review, including review by the relevant program centers.

Tier Two Comments

The Tier Two Process Should Be More Timely And Predictable. PhRMA supports the creation of an expert Dispute Resolution Panel (DR Panel) to review scientific and technical disputes that cannot be resolved at the Tier I level. PhRMA is concerned, however, that the Tier II procedure described in the Draft Guidance may not render decisions in a timely manner. According to the Draft Guidance, if an issue is appropriate for review, the DR Panel "will bring the issue to the next scheduled DR Panel meeting for which there is time available on the agenda." There is no requirement that the DR Panel schedule a meeting within a certain time frame of receiving a dispute resolution request (e.g., 60 days) or even conduct meetings at regularly scheduled intervals (e.g., every 3 months). PhRMA is thus concerned that the timing of a Tier II decision will not be predictable and that decisions themselves may be significantly delayed based upon the vagaries associated with scheduling *ad hoc* meetings. This lack of predictability and timeliness could dissuade companies from utilizing the Tier Two process, especially given the time sensitive nature of many cGMP issues. PhRMA thus requests that FDA include a time limitation of sixty (60) days for DR Panel review of Tier II dispute resolution request to make the process more timely and predictable.

FDA Should Clarify The Composition of the DR Panel. The Draft Guidance states that the DR Panel will consist of "representatives from each of the program centers . . ." FDA should provide additional information clarifying which program center officials will serve on the DR Panel. To serve effectively, DR Panel members must have a broad range of expertise in cGMP issues. In addition, it is not clear whether representatives from the Chief Counsel's office or the Office of Regulatory Affairs will

be included in the DR Panel as suggested in the original concept paper issued by FDA on the dispute resolution process.

The Draft Guidance also states that, “[i]f necessary, additional experts may be added to the DR Panel to facilitate evaluation of the specific issue.” PhRMA supports the use of experts to provide specialized knowledge about particular scientific and technical cGMP issues that arise during panel review. FDA should clarify, however, whether these experts will be internal experts (i.e., FDA employees), external experts, or both, and how they will be chosen.

General Comments

Confidential Information Should Be Protected. PhRMA supports FDA’s proposal to publish decisions reached during Tier I and Tier II that provide valuable guidance to the regulated industry. In publishing such decisions, however, care must be taken to protect and redact confidential commercial information and trade secrets, particularly with respect to innovative manufacturing processes. Much of the information associated with cGMP disputes may be particularly sensitive manufacturing information that rises to the level of trade secrets. Before publicly disseminating any information, consultation with the affected company in accordance with FDA’s Freedom of Information Act regulations should be required.

In addition, in cases where the ORA unit agrees with the manufacturer, there is no indication that information will be redacted prior to public dissemination. The Draft Guidance should be revised to indicate that proper redaction, including consultation with the affected company, will take place prior to public dissemination.

The “Administrative Record” Should Include All Information Submitted In The Initial Dispute Resolution Request. The Draft Guidance states that agency decisions generally will be “based on the manufacturer’s administrative record that was available at the time of the inspection” and that “[n]o new information should be submitted as part of a request for formal dispute resolution.” While PhRMA agrees that Tier II decisions should be based solely upon the information submitted as part of the Tier I process, including information submitted to the Center in response to the district’s decision, there is no basis for restricting the information that can be relied upon during the formal dispute resolution process to that available and submitted during the inspection.

The inspection process is too informal to serve as a basis for imposing such draconian administrative penalties during the formal dispute resolution process. Relevant information may not be provided during an inspection for a number of reasons, including lack of time; lack of clarity; miscommunication; lack of expertise; shifting requests and priorities by the inspector; or a hesitation by company personnel to challenge an inspector. Moreover, the inspector’s concerns often are not

communicated to the company or fully understood until crystallized in the form of a 483. While PhRMA certainly supports efforts to encourage the resolution of disputes informally during an inspection, PhRMA believes this proposed penalty is both unnecessary and unfair. This is especially the case given that (a) FDA inspectors are not required to utilize informal dispute resolution and (b) the Draft Guidance provides virtually no guidelines on how informal dispute resolution should operate.

In addition, the Draft Guidance's "administrative record" requirement may block FDA from considering the most relevant data and information on the particular issue under dispute. This will result in suboptimal and/or incorrect Agency decisions on important scientific and technical issues, which, if publicly disseminated, could become suboptimal and/or incorrect Agency precedent. PhRMA believes that FDA's overriding goal in the dispute resolution process should be to reach correct scientific and technical decisions on cGMP issues. The Agency's desire to encourage informal dispute resolution, while also important, should not undermine this primary goal. Accordingly, the Agency's decisions during the formal dispute resolution process should be based upon all information submitted during the Tier I process, even if that information was not presented or available during the inspection.

The Formal Dispute Resolution Process Should Be Available For All Scientific And Technical Issues Raised In The 483. Section IV.B. of the Draft Guidance states that "[i]n 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." According to the Draft Guidance, a manufacturer must demonstrate that it was "unable to raise its disagreement during the inspection" in order to become eligible for the formal dispute resolution process. PhRMA believes that this entire subsection is unnecessary and unfair and should be deleted.

While PhRMA believes that both companies and FDA should be encouraged to resolve disputes early and informally during the inspection process, this should not be a prerequisite for utilizing formal dispute resolution procedures after the issuance of a 483. Just as FDA clarifies that the observations in a 483 are not final agency decisions but rather the opinion of an individual inspector, so FDA should recognize that the response of an individual site manager during an inspection may not represent the final position of the company as a whole. A specific site may not raise an issue for a number of legitimate reasons as discussed above, including because they do not understand the global implications of the issue for the company. Companies thus should have the ability to review 483 observations for company-wide implications and to challenge those findings through the formal dispute resolutions procedures even if the individual site has not raised a particular issue during the inspection.

Moreover, limiting the availability of the formal dispute resolution process in this manner is not fair because it requires only one party – companies -- to utilize informal dispute resolution but not FDA inspectors. The Draft Guidance states that the FDA

investigator "can consult" with scientific or technical experts or FDA management "as appropriate," but there is no requirement to do so. Moreover, there are no established procedures for informal dispute resolution during an inspection. Given these factors, it is not appropriate to make informal dispute resolution a prerequisite for initiating the formal dispute resolution process. If FDA wishes to maintain this principle, it should (a) make informal dispute resolution mandatory for both manufacturers *and* FDA inspectors, and (b) establish a standardized procedure with fixed timelines for review and decisions.

In addition, this requirement is likely to generate disputes as to whether a manufacturer did or did not raise a particular issue during an inspection and/or whether a particular issue was communicated clearly by FDA during the inspection. PhRMA believes that the dispute resolution process should focus on resolving legitimate scientific and technical issues, not generating intractable procedural issues that have the potential of devolving into "he said/she said" disputes.

Regulatory Action Should Generally Be Delayed Until A Dispute Is Resolved. The Draft Guidance indicates that FDA "may take regulatory action under appropriate circumstances while a request for formal dispute resolution is pending." PhRMA believes it would be helpful for FDA to clarify what it means by "appropriate circumstances." In general, PhRMA believes that FDA should decline taking regulatory action with respect to an issue under review until the dispute has been resolved. Thus, FDA should clarify that it generally will not initiate regulatory action while a request for formal dispute resolution is pending but may take action (a) if the issue involves an immediate health risk, or (b) with respect to issues that have not been disputed.

Thank you for your consideration of these comments.

Sincerely,



Scott M. Lassman
Assistant General Counsel