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

Re: Draft Guidance on Formal Dispute Resolution: Appeals Above the Division Level (Docket No. FDA-2013-D-0221)

Dear Sir or Madam:

On September 9, 2015, the Food and Drug Administration (FDA) issued a notice seeking comments on a revision of its draft guidance entitled "Formal Dispute Resolution: Appeals Above the Division Level, Guidance for Industry and Review Staff" (the 2015 Draft Guidance). The 2015 Draft Guidance describes a structured procedure at the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for formally appealing medical or scientific disputes between the review divisions within those centers and members of regulated industry.

Our firm represents numerous sponsors, applicants and manufacturers who develop products regulated by CDER and CBER and who, on occasion, seek to use the Formal Dispute Resolution (FDR) process to ensure open, prompt evaluation of medical or scientific disagreements with the review divisions. Since issuance of the first FDR guidance in 2000, our firm has drafted dozens of FDR requests for clients and has also advised numerous other clients that pursuing FDR was not advisable based on the facts or circumstances of their cases. Our experience with the FDR process, including the benefits of early input above the division level, positions us to fully appreciate the implications of what may seem like small changes between the 2015 Draft Guidance and the earlier 2013 version (the 2013 Draft Guidance).

BACKGROUND

The FDR process grew out of the Agency's 1998 implementation of section 562 of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), which directed FDA to

ensure that it had adequate dispute resolution procedures to address scientific and/or medical controversies related to products regulated by CDER and CBER. Such processes are critical in that they permit complex matters, where there may be scientific disagreement, to be vetted by senior drug development officials whose breadth and depth of experience provide perspectives and solutions that might not otherwise be considered.

On March 7, 2000, FDA issued a final guidance document describing the procedures that CDER and CBER would use for resolving scientific and procedural disputes that cannot be resolved at the division level (the 2000 Final Guidance). On March 13, 2013, FDA issued the 2013 Draft Guidance, which updated the 2000 Final Guidance significantly by setting forth various limitations regarding when the FDR process could be utilized.

On September 9, 2015, FDA issued the 2015 Draft Guidance, which differs from the 2013 Draft Guidance, in several respects. This comment focuses on one aspect of the 2015 Draft Guidance which we see as adding an unnecessary obstacle to the prompt and efficient resolution of medical and scientific disputes above the division level by further limiting the types of matters that would be considered appropriate for an FDR request.

SCOPE OF MATTERS FOR AN FDR REQUEST

According to the 2015 Draft Guidance, "advice communicated in meeting minutes and general advice letters is not a regulatory action taken by CDER or CBER, so it would not be an appropriate subject for an FDR request."[1] While the 2013 Draft Guidance was silent on this issue, our firm has participated in FDR processes based, in large part, on positions taken by review divisions in meeting minutes. We therefore believe this is a substantive change in the FDR process.

Development stage FDA-sponsor meetings are held largely to obtain FDA input on the adequacy of existing and planned studies or data to achieve some regulatory purpose. Among other purposes, these meetings may be related to adequacy to initiate acute or chronic dosing in clinical trials, adequacy to initiate another phase of development or adequacy for application review.

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[1] See lines 150-152 on page 5 of the 2015 Draft Guidance: Formal Dispute Resolution: Appeals Above the Division Level, Guidance for Industry and Review Staff.

End-of-Phase 2 (EOP2) meetings are particularly critical in this regard. Such meetings are "directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed." 21 C.F.R. § 312.47(b)(1)(v). In recognition of the importance of reaching key agreements prior to initiation of Phase 3, FDA's regulations note that EOP2 meetings "should be held before major commitments of effort and resources to specific Phase 3 tests are made." 21 C.F.R. § 312.47(b)(1)(iii). In the spirit of this regulation, the FDR process should be available, in cases of disagreement between the sponsor and the review division, to increase the likelihood of agreement prior to expenditure of significant resources.

While the outcome of a meeting may not be a "regulatory action" as that phrase is used in the 2015 Draft Guidance, it is an agreement - or lack of agreement - on an important topic that may significantly affect development of the product at issue. An inability to appeal through the FDR process leaves sponsors with the untenable choice set forth in the 2015 Draft Guidance: follow the advice in the meeting minutes or use an alternative approach "if the approach satisfies the requirements of the applicable statutes and regulations." Of course, this is the key question: whether the alternative approach being proposed by the sponsor does in fact meet the legal requirements – requirements that will be interpreted at the moment of a regulatory action by the review division or office, which has already carefully considered the issue and set forth its view in meeting minutes.

A simple example illustrates the point. At an EOP2 meeting, a sponsor proposes that the pivotal Phase 3 studies for its drug utilize a certain endpoint and asks whether the review division agrees. The meeting minutes accurately convey the division's disagreement with language such as "No, we do not agree. In order for your studies to provide substantial evidence of efficacy, we strongly recommend that you demonstrate an improvement over placebo in [insert FDA-preferred endpoint]." Further discussions with the division suggest that the disagreement cannot be resolved. Absent the ability to appeal above the division, the sponsor has the two choices set forth above: follow the advice in the meeting minutes or use an alternative approach. The example is best understood by investigating the downstream risks of the two choices:

- Under choice number one, the sponsor follows the advice in the meeting minutes despite its belief, and the advice of its experts, that the FDA-recommended endpoint is fraught with potential for variability and error. The sponsor invests significant resources into the Phase 3 studies only to have them fail because of the predicted variability. At this point, the sponsor still

cannot obtain higher level adjudication on use of the alternative endpoint because it has no final regulatory action on endpoint selection. It would have to follow the path outlined for choice number two below in order to be eligible for FDR on the question of the endpoint.

- Under choice number two, in which the sponsor utilizes its originally planned endpoint, the study may not be fundable because of the existence of FDA meeting minutes strongly disagreeing with a key pivotal study design element. If the funding can be secured and the studies are successful on the chosen endpoint, the sponsor is already on notice that the review division will not consider these studies sufficient to demonstrate efficacy. It will request a pre-NDA meeting at which the division is likely to restate its view and refer back to the EOP2 minutes noting that the sponsor failed to follow previous advice. The sponsor, still unable to avail itself of the FDR process, must spend the resources necessary to prepare and submit a marketing application, and pay a user fee in excess of $2,000,000. FDA may issue a refusal to file (RTF) letter, which will restate that the endpoint is not appropriate. Because the FDR process is not available for RTF actions, the sponsor must file over protest. Whether the application is voluntarily filed by FDA or filed over protest, the sponsor must wait 10 additional months, and face the prospect of an advisory committee which will consume significant additional resources, prior to receiving a complete response letter (CRL) stating for at least the fourth time that the endpoint was inappropriate. An appeal is still not available. The sponsor must instead request and attend another meeting with the division at which it will, for the fifth time, be told (likely with some warranted frustration by the review division) that the endpoint is not appropriate. Only at this point, three to four years after the original disagreement with the division, can the sponsor appeal under the 2015 Draft Guidance. If the appeal is successful in determining that the alternative endpoint is appropriate, the sponsor must assemble an NDA resubmission and undergo another six month review clock.

In either case, much was wasted: large numbers of patients participated in unnecessary placebo-controlled trials, years of patent life on the product were lost and millions of dollars were spent on trials and submissions that could have been avoided had the FDR process been available at the moment of disagreement on this critical issue.

Rather than selection of a Phase 3 endpoint, the disagreement, memorialized in meeting minutes or a general advice letter, could involve matters such as the statistical

method for handling missing data, the need for carcinogenicity studies or the adequacy of impurity characterization. In any of these cases or a panoply of additional illustrations that could be listed, a sponsor who fails to follow review division advice (or follows advice that it believes is faulty) is at significant peril. In these cases, the FDR process can serve as an invaluable tool for appropriate de-risking of drug development. This de-risking has the greatest benefit for novel therapies that are designed to address unmet medical needs as those are the areas in which study design and other issues are not yet well settled and would benefit the most from the perspective of senior FDA officials whose experience permits the broadest consideration of possible options.

CONCLUSION

We hope to have demonstrated that a failure to resolve such disputes efficiently and effectively has the palpable potential to hinder the availability of promising drugs and biologics and, ultimately, public access to them – sometimes for many years and sometimes forever.

We note that FDA has numerous bases on which it can refuse to accept an FDR. The fact that an important disagreement is memorialized in meeting minutes or a general advice letter should not be one of them. We submit these comments seeking deletion of lines 145-152 from the 2015 Draft Guidance such that some advice communicated in meeting minutes and general advice letters continues to be included in the ambit of subject matter eligible for an FDR request.

Like all guidance documents, the 2015 Draft Guidance notes that draft guidances merely "describe the Agency's current thinking on a topic and should be viewed only as recommendations…" and "are not binding on FDA or the public." Our experience with the 2013 Draft Guidance, however, teaches that an FDR request that failed to comply with any aspect of that document was rejected by the FDR coordinator and not permitted to be heard. We therefore expect that the additional limitations set forth in the 2015 Draft Guidance have already been implemented and could currently prevent acceptance of FDR requests. As a result, we also request that FDA continue to hear FDRs based on a dispute set forth in meeting minutes or general advice letters until it has formally considered the comments in this docket.

Should you have any questions or desire clarifying information, please contact me at jtorrente@hpm.com or at (202) 737-7554.

Sincerely,

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for FJS

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