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PhRMA

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

RE: Docket No. 2003N-0472; Statement of Work for the Evaluation of First Cycle Review Performance; 68 Federal Register 60108

Dear Sir/Madam:

The following comments on the Statement of Work for the Evaluation of First Cycle Review Performance (SOW) are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

During the industry/FDA discussions leading to the reauthorization of the Prescription Drug User Fee Act (PDUFA), PhRMA noted that it is critical to look at some of the structural issues related to the drug review process with a goal of identifying factors that can improve the possibility of first cycle approvals of new NDAs. FDA has already implemented the 74 day letter, designed to provide drug sponsors with a preliminary identification of substantive deficiencies, and issued a draft set of Good Review Management Principles (GRMPs). PhRMA also was willing to commit a portion of the PDUFA-III Fees for outside review activities that could assist the Agency in improving the drug review process. This SOW is part of that PDUFA-III agreement. PhRMA's comments follow in the sections below.

GENERAL COMMENTS

1. It is important for the industry to be included as a key participant in every aspect of this endeavor, and we are pleased that the sample SOW provides for evaluation from the perspective of applicants as well as the FDA. Such involvement is essential to provide the contractor with the necessary insight to understand the complexity of preparing applications for submission and to avoid misleading misconceptions.

2. PDUFA goals and the sample SOW are unclear with regard to targeted initiatives undertaken by the Agency that will be evaluated on the ability to enhance the first cycle review performance. There is an implication that issuance of an approval letter on or before

the first cycle PDUFA date is the only outcome of interest.[1] If there are outcomes other than first cycle approval that are considered representative of good review management, it may be useful to describe them in the SOW. For example, for reviews that did not result in a first cycle approval, whether or not early notification of issues identified during the filing review was provided to the applicant may be a useful measure; whether discipline review letters were issued and, if so, the timing of their issuance with respect to the disciplines represented by the deficiencies cited in the action letter may provide useful information; whether (and how much) time was available for labeling and post-marketing commitment negotiations in the first review cycle might be considered helpful; and for applications that require advisory committee review, parameters related to the timing of that decision, notification of the applicant, and pre-advisory committee consultation between the agency and applicant may be useful in assessing first cycle review performance as well as suggesting procedural revisions to improve it.

3. The PDUFA goals set forth ambitious objectives for the evaluation of first cycle review performance including evaluation of current performance, evaluation of the effectiveness of the FDA training program, and assessment of the changes that occur after the guidance on GRMPs is published. Although FDA agreed to create GRMPs that apply to all NDAs, BLAs, and efficacy supplements, Section X.D. (Evaluation) of the PDUFA goals limits the scope of the evaluation to BLAs and NDAs for NMEs, thereby limiting both the population of applications available for evaluation and the applicability of the results. Thus, a large number of variables must be assessed (different review divisions, changing baseline as new recommendations are implemented, varying complexity of applications and issues) on the basis of a limited number of reviews of a sample sub-population of applications that is, by definition, not representative of all applications. At best, only highly subjective conclusions that have limited applicability will be possible from such a limited evaluation.

   The usefulness of the evaluation would be improved by including all NDAs, efficacy supplements, and BLAs in the evaluation of both baseline (current) performance and performance during PDUFA III. This would obviate limits imposed by relying on the smaller sample of unique applications that are clearly not representative of all applications. Because, rather than a sample, the entire population of applications intended to be affected by GRMPs would be included in the evaluation, direct conclusions regarding changes after the GRMPs were published would be possible. Furthermore, performance with respect to subgroups such as NMEs, standard reviews, and priority reviews could be evaluated and reported. In addition, a comprehensive evaluation of all NDAs, efficacy supplements, and BLAs would obviate the potential for observer bias to influence the conclusions.

4. The agency's draft guidance document on GRMPs[2] describes many current processes and procedures that are followed in at least some review divisions. Because of the small sample size imposed by focusing on NMEs and BLAs only, unless there is a wide disparity between Review Divisions on current practices, it will be difficult under the proposed SOW

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[1] See Page 1, Section A, Second Paragraph: "For applications that otherwise meet the standards for approval, the process allows for finishing the review of the labeling and other regulatory issues (e.g., negotiation of postmarketing commitments) and issuance of an approval letter on or before the PDUFA goal date, thereby eliminating unnecessary, inefficient additional cycles."

[2] "Draft Guidance for Reviewers and Industry on Good Review Management Principles for Prescription Drug User Fee Act Products", Docket 2003D-0317 (68 FR 44345, July 28, 2003)

to identify any overall improvement or deterioration in first cycle review performance, much less ascribe any observed change to specific GRMPs.

SPECIFIC COMMENTS

B. Key Objectives

B.1. Although the study is designed to include an assessment of current performance, PhRMA notes that the sample SOW limits the retrospective analysis of NMEs and BLAs to those submitted in FY 2002. This minimalist approach does not follow scientific standards, and it is bound to generate skewed results. Such a small database is inadequate to develop an appropriate evaluation criteria upon which to base future assessments of the Agency's performance during the next 5 years.

Additionally, the retrospective analysis is too limited to gain an accurate measure of current performance across the CDER review divisions and CBER. One of the historical concerns of industry is inconsistent working policies and practices between CDER Review Divisions and between CDER and CBER.

PhRMA recommends that the assessment of current performance should include a sufficient number of applications reviewed under PDUFA performance criteria so that all CDER review Divisions are appropriately represented with respect to handling Priority (P) and Standard (S) applications. A more expanded sampling will provide not only a more accurate reflection of performance across the Agency, but will also reflect greater diversity with respect to applicants. Since the primary goal of the study is to evaluate the impact of FDA's implementation of initiatives to enhance first cycle review performance during the five-year period of PDUFA III, PhRMA recommends that a retrospective analysis of performance over the 3-5 years preceding PDUFA III is more appropriate as a base-line measure.

Consistent with the PDUFA III performance goal letter (section X.D.1.), the retrospective evaluation of current performance should also include *both* the FDA and industry perspective. This objective is mentioned in the *Scope of Work* section of the SOW; however, as a point of emphasis to the contractor, we recommend that the objectives explicitly note the goal of obtaining input from both the Agency and industry as part of the objectives.

The therapeutic classification of the applications (P versus S) and activities covered by regulatory mechanisms such Fast Track designation, development under the provisions of 21 CFR 312 Subpart E, and accelerated approval under the provisions of 21 CFR 314 Subpart H also can significantly impact current first-cycle performance. Accordingly, it is important that results of the retrospective and prospective assessments be appropriately stratified to reflect this information.

PhRMA also recommends categorizing the reasons for multiple cycle reviews by discipline (i.e., CMC, Pharmacology/Toxicology, Clinical, etc.), and by Division. This would allow FDA to evaluate whether trends exist (i.e., the majority of products were held up by a similar issue, and/or is one Division problematic in a specific area).

B.2. Please see the comment above regarding our recommendation to stratify results by therapeutic class and applications associated with development or approval under mechanisms intended to expedite the availability of treatments for life threatening or severely debilitating illnesses. Please also note our comments regarding the need to emphasize that both the perspectives of the FDA and applicants should be included in the assessment.

B.3. CDER can harvest important lessons about first cycle performance by also evaluating the following:

- Comparing first-cycle performance among each of its 15 reviewing Divisions;
- Comparing first-cycle performance between Centers;
- Conducting systematic interviews with a sample of Divisions that have a high percentage of first-cycle approvals versus a sample of Divisions with a low percentage of first-cycle approvals.

C. Scope of Work

The third paragraph of the *Scope of Work* section, states:

"For the first cycle review of applications, the contractor should assess the interactions between FDA and the applicants by examining documents and by observing events in the review process. The contractor should draw on many sources of information, such as FDA tracking databases, participation in review events, direct feedback through interviews with FDA and applicant staff, and other records of review activity."

PhRMA recommends that this section of the document explicitly state that FDA and applicant staff should be given an opportunity to review and comment on the preliminary summary findings of the review performance. Additionally, it should state that the consultant should develop a standard set of questions and definitions that would be used when obtaining input from FDA and applicants. The instrument should address key development activities, i.e., occurrence of milestone meetings, use of Special Protocol requests, definition of measures of application quality, whether manufacturing facilities were PAI ready and passed inspection, etc.

The SOW also states that the evaluation will include *"prospective and retrospective analyses of review process management, communication...and other factors...."* It also notes that, *"...the contractor should assess the interactions between FDA and the applicants by examining documents and by observing events in the review process. The contractor should draw on many sources of information, such as FDA tracking databases, participation in review events, direct feedback through interviews with FDA and applicant staff, and other records of review activity."*(Emphasis added) The PDUFA goals, however, appear to envision only a retrospective analysis.[3] While a prospective analysis could be conducted without the data collection process influencing the conduct of the review, it is unlikely that direct contractor observation of events in

[3] "The study will also include an assessment of the first cycle review *history* of all NDAs for NMEs and all BLAs during PDUFA 3. This assessment will include a more detailed evaluation of events that *occurred* during the review process with a focus on identifying best practices by FDA and industry that facilitated the review process." (Emphasis added) (2002 Prescription Drug User Fee Act (PDUFA) Performance Goals, Section X.D.2.)

the course of the review and contractor participation in events are possible without influencing the process the contractor is retained to evaluate. PhRMA recommends that direct contact between the contractor and the review team (including the Division Director and Office Director) should be avoided during the course of the first cycle review to avoid bias.

D. Key Tasks

D. 1. The assessment of baseline performance, including the search for potential root causes, and the description of the scope of the evaluation of applications submitted during PDUFA III should include events, communications, actions, and interactions that did or did not take place under the IND (i.e., end-of-phase 2 advice, special protocol review conducted or denied, and other opportunities for interaction).

D.2. PhRMA recommends adding the following statements under *sample evaluations*:

- Effectiveness of FDA review schedule, degree to which the review was transparent to the applicant (i.e., sharing of FDA interim review targets, use and role of FDA internal consultants, use and timing of advisory committee meetings);
- Consistency of practice between FDA review Divisions/Centers in following established MAPPs, adherence to prior agreements with sponsors as documented in meeting minutes, continuity of review team assignments with reviewers during IND phase, direct dialogue between reviewers and appropriate applicant personnel to resolve outstanding questions.

D.4. The introduction and implementation of GRMPs will overlap with other initiatives that may have an impact on first cycle reviews such as the submission of applications in accordance with CTD and eCTD recommendations and the risk-based approach to pharmaceutical current good manufacturing practices. It may be helpful to stipulate in the SOW the need to keep track of these and other programs that may influence first cycle review performance that are implemented concurrently with the GRMP initiative during PDUFA III. This would enable the contractor to consider the potential influence of such programs in drawing conclusions.

D.5. Because the contractor is responsible for evaluating FDA training as well as the impact of changes introduced, the SOW should describe how FDA will provide feed-back to the contractor on its initiation of recommended changes, including the staff training necessary to implement the change.

D.6. Key Task 6 states that actions will be recommended on a continuous basis to improve first cycle review performance. In this section, it also states that "*preliminary recommendations will be summarized for FDA management on a yearly basis, etc.*" PhRMA recommends clarifying whether the *"continuous recommendations"* referred to in Key Task 6 are, in fact, the annual summaries, or whether the annual summaries are a compilation of the continuous recommendations made during the prior year. In the latter case, to whom are the continuous recommendations made?

Key Task 6 also indicates that the contractor will provide continuous recommendations that include activities pertinent to both FDA review staff and applicants. PhRMA recommends that

in addition to providing FDA management annual interim reports, provisions should be added for communicating preliminary information to industry along with an opportunity for feedback

In addition to the above comments, PhRMA recommends that the following Key Task be added: Assess differences in review practices and FDA-applicant interactions for priority and standard applications.

E. Deliverables

E.2. The PDUFA Goal at Section X.D.6 states that, *"...the Office of the Commissioner will convene a joint CDER/CBER review panel on a quarterly basis as a mechanism for ongoing assessment of the application of Good Review Management Principles to actions taken on original NDA/BLA applications."* Section E.2. of the SOW describes, *"Periodic briefing(s) to the PDUFA III Implementation Steering Group"* but does not mention the CDER/CBER review panel. The final SOW should clarify whether these are two distinct groups and, if so, the roles and responsibilities of the contractor to each.

Additionally, PhRMA recommends that annual reports should also be available to the public for review.

PhRMA trusts that these comments are useful to FDA as the Agency moves forward to finalize this important SOW. Please do not hesitate to call me if there are any questions associated with these comments.

Sincerely,