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PhRMA

July 31, 2003

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

RE: Docket No. 2003D-0229: Draft Guidance for Industry on Continuous Marketing Applications: Pilot 2--Scientific Feedback and Interactions During Development of Fast Track Products Under the Prescription Drug User Fee Act

Dear Sir/Madam:

The following comments on the above noted draft Guidance document are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA).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.

PhRMA values the work FDA has put into this draft Guidance and appreciates the opportunity to comment. PhRMA hopes this consolidated set of industry comments will permit FDA to meet is goal of initiating this Pilot program in October 2003.

General Comments/Statement

PhRMA commends FDA for its continued attention to innovative ways to improve the efficiency of the drug development and approval process. Specifically, PhRMA applauds FDA's agreement, under the performance goals that accompanied the June, 2002, reauthorization of the Prescription Drug User Fee Act (PDUFA goals), to formally explore the concept of the "continuous marketing application" in the form of two pilot projects. Under "Pilot 1" FDA agreed to evaluate the costs and benefits of early review of parts of a marketing application, while under "Pilot 2" the agency will evaluate the impact of frequent scientific feedback during the IND phase of drug development.

According to the PDUFA-III agreement between industry and the FDA, Pilot 2 is limited to one fast track product per CDER and CBER review division. PhRMA agreed to this because both the amount of needed FDA resources and the results of the Pilot are unknown. However, as PhRMA noted during the discussions leading up to the agreement, FDA should have the discretion to increase the number of products eligible

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for this pilot if it appears that there is not a significant drain on review division resources and that the Pilot is succeeding in shortening the drug development and review time line.

Specific Comments

Section III. Pilot 2 Implementation
Section III. A. Selection of Participant Drug and Biological Products
Section III.A.1. Eligible Drug and Biological Products

While PDUFA allows for one Fast Track product per review division in the Pilot, it is likely that not all Divisions will be able to participate given the current criteria. In addition to PhRMA's general comments on Pilot expansion, the guidance should allow for the opportunity to expand the Pilot if there are cases where the interaction would provide obvious benefit. For example, many Divisions have several therapeutic classes within their respective areas of responsibility. Consideration could be given to providing an opportunity to expand the Pilot to include more than one application per Division.

Section III. A. 2. Pilot 2 Implementation - Application Process:

The application process outlined in the draft guidance requests information, justification, and a draft agreement for proposed feedback and interactions with FDA. The information requested includes, among other things, a summary of the End-of-Phase 1 meeting, a timeline of milestones for product development, and an overview of product development with information for each review discipline. In addition, applicants are requested to write a rationale for their participation in which they specify ways in which the development of the product would be improved by enrollment in Pilot 2 and the potential for frequent communication to benefit the public health by improving the efficiency of the drug development program.

These "requirements" go far beyond the eligibility requirements described in the PDUFA goals and create an unnecessary workload burden for both industry and FDA. Applications are eligible for consideration for Pilot 2 if the products have been designated for expedited development under the fast track program and have been the subject of an End-of-Phase 1 meeting. The only additional requirement should be a commitment on the part of an applicant to product development under the conditions to be agreed upon with the review division under Pilot 2. The additional information and rationale requested appear to be aimed at allowing the FDA to select applications that it believes would benefit the most from participation in the pilot and, as a result, benefit the public health. This presumes benefit and, therefore, may bias the outcome of the Pilot by creating an imperative to show value. It may be, especially in view of the formal agreement requirements under Pilot 2, that fast track applications processed in the manner FDA has employed on an ad hoc basis since FDAMA was enacted in 1997 will be more effective in promoting drug development.

For eligible applications, the only other requirement for successful evaluation of frequent scientific feedback and interactions with FDA during the drug development

process is a sponsor committed to development of the product under the conditions of Pilot 2. PhRMA recommends that the "requirement" for submission and review of extensive information in the form of a Pilot 2 application be reconsidered. Applications should be invited that contain a request for consideration and a commitment to abide by the conditions necessary to conduct Pilot 2. Applications may be accepted on a first come-first serve basis and an announcement made when a review division has accepted an application for enrollment. Alternates may be identified in the event the Division and originally selected applicant are unable to reach agreement on the nature and timelines for feedback (as provided for in Section III.B.)

Section III. A. 4. Application Timeline and Applicant Notification
The application timeline proposed in the draft guidance is the 2 month window beginning October 1, 2003 and ending November 30, 2003. This effectively confines the program to INDs that have already been designated under the fast track program and have already been the subject of an end of phase 1 (or equivalent) meeting because, even for already designated applications, there would not be time between now and October 1, 2003 to schedule the prerequisite meeting.

For the initial round of applications, it appears that FDA intends to collect all applications for Pilot 2, review them, and make its selection for each division from the entire Pilot 2 application pool. For Divisions that have not received an acceptable application by November 30, 2003, a "first come - first served" approach is planned. Although the draft guidance says that applications will continue to be accepted through September 30, 2004, it also notes that the first application received that adequately meets the evaluation criteria will be accepted and selected applicants will be informed within 3 months of application submission. Clearly, therefore, applications will not be accepted through September 30, 2004 unless there happen to be no successful candidates through that date. PhRMA recommends that FDA consider ways to publicly announce the closing of a Division's application process prior to the September 30, 2004 date to inform potential applicants that applications are no longer being accepted.

Section III. B. Agreement on Feedback and Interactions
1. Paragraph 1
a) With respect to agreements between the applicant and FDA and the provision to make changes by subsequent agreement, there needs to be liquidity in the approach to methods of communication. Circumstances may dictate an unforeseen and urgent communication need that is important to the statutory mandate to expedite fast track applications but that falls outside of the timelines or triggering events documented in the existing agreement.
b) The draft guidance states, *"If, after reasonable attempts to negotiate, the review division and the applicant are unable to finalize the agreement, the review division may notify the applicant in writing that the product will not be entered into Pilot 2, and the review division may select another application for Pilot 2."*

If it is FDA's intention that this decision by the review division is not subject to appeal through dispute resolution, the final guidance should specifically make that point.

2. Under "Applicant Submissions" the draft guidance repeats the discussion of study reports appearing in PDUFA Goals VII(B)(3) to provide examples of submissions that will stimulate feedback between the applicant and FDA. It states, *"Decisions regarding which study reports will be reviewed as study summaries or draft study reports and which will be reviewed as complete study reports will generally be made as part of the agreement. Such decisions will be based on the importance of the study to the development program, the nature of the study, and the potential value of limited (i.e., based on summaries or drafts) versus more thorough (i.e., based on complete study reports) division review."*

In general, during the course of development, a full study report is not routinely prepared upon completion of a study. Instead, the study is analyzed and the results evaluated with respect to moving forward with the overall development plan. Any expectation for a full study report before interaction between the applicant and the agency will slow rather than facilitate development. PhRMA recommends that if the reference to full study reports is retained, the final guidance should clarify that such reports would rarely be necessary and that review divisions and applicants should seek agreement on alternative ways to share and discuss results.

3. Special protocol assessments also are discussed under the bullet "Applicant Submissions", which provides examples of the types of submissions that an applicant and FDA may agree upon as triggers for feedback and interactions..

FDA should clarify whether, under Pilot 2, the timelines and procedures for special protocol assessments are the same as for other applications or whether the applicant and the division may agree to alternative procedures or timelines.

4. PhRMA recommends that the guidance for Pilot 2 emphasize the need to set aggressive timelines for responses from both industry and FDA in planning and scheduling meetings and documenting agreements

5. Paragraph 3
a) The last paragraph in this section addresses periodic re-evaluation of each agreement by each review division to determine whether the agreement "continues to promote the goals of Pilot 2". Among the conditions that may "necessitate termination of an agreement" are *"significant disagreements in approach to product development between the applicant and review division, or significant deviation by the applicant from the development plan negotiated with the review division."*

First, it is unclear whether "termination of an agreement" as used in this context means termination from Pilot 2. Second, both of the conditions described in this sentence have implications for the application under the fast track program exclusive of implications for Pilot 2. For example, how would the review division fulfill the statutory mandate to "facilitate the development and expedite the review of" a fast track product for which it had terminated the agreement under Pilot 2? Third, the language of the draft guidance appears to grant authority to terminate an agreement to the review division. There is no mention of whether such an action on the part of the review division would be subject to review at a higher level within the Center or subject to a dispute resolution procedure.

Because of the potential importance of products that have qualified for fast track designation, an applicant subject to a decision by the review division to terminate either the Pilot 2 agreement or participation in Pilot 2 should be afforded an opportunity for review at higher levels within the Center.

b) PhRMA recommends inclusion of a statement indicating that all Divisions will review their agreements at least annually to minimize major discrepancies between Divisions with regard to the frequency of the planned re-evaluations.

Section III.C. Pilot 2 Evaluation, Reporting and Conclusion

1. Paragraph 1 The draft guidance states that Pilot 2 agreements and activities for each application will continue through September 30, 2007 unless one of various conditions occurs. If the fast track development program should continue beyond the end of the Pilot (September 30, 2007), it is not clear whether the sponsor immediately loses the benefit of the Pilot 2 agreements and activities on this date. PhRMA recommends the guidance clarify what will happen in this situation.

2. Paragraph 2 The Guidance should be revised to include a statement that the independent expert consultant will protect the confidentiality of the applicant's information.

3. As agreements between FDA and the applicant need to be negotiated it will be important to specifically track the time it takes to accomplish this as part of the evaluation of this Pilot.

4. A great deal of flexibility is allowed in Pilot 2 in terms of the design of the written agreement between the Division and applicant. While this will help maximize the value of the program, it will be important for the evaluation to include an assessment of the variability of the agreements across Divisions and the impact such variability has on the cost of the interactions and the efficiency and effectiveness of the development programs.

5. The CMA Pilots were developed under PDUFA III as a means to further shorten drug development and review times. As PDUFA will next be reauthorized in 2006, feedback on the CMA Pilots as currently designed will not be available for incorporation into PDUFA reauthorization discussions. We encourage the Agency to reconsider the timing of the consultant report with a goal of having at least preliminary feedback on the Pilots available no later than the end of calendar year 2005.

Other comments

1. Neither this draft guidance nor the draft guidance for Pilot 1 (Draft Guidance for Industry on Continuous Marketing Applications: Pilot 1--Reviewable Units for Fast Track Products Under the Prescription Drug User Fee Act, 68 FR 35903) indicates whether applications enrolled in Pilot 2 (scientific feedback) will be eligible (or, perhaps given preference) for enrollment in Pilot 1 (early review). PhRMA believes that, if circumstances permit, important information may be gleaned from evaluating the results of exposure of applications to both continuous marketing application projects. Our specific comments on Pilot 1 are the subject of a separate letter to Docket No. 2003D-0228.

2. The draft guidance notes that FDA will use an independent expert consultant to evaluate the Pilot. It would be useful to identify the consultant far enough in advance of implementing the Pilot to allow input into the design of relevant aspects of the program. It may also be useful to have the consultant review the selection criteria for applications to ensure consistency across review divisions and centers for the purposes of this Pilot.

PhRMA hopes that these comments are useful to FDA as the Agency moves forward to finalize this guidance. Please do not hesitate to contact me if there are any questions.

Sincerely,

Alan Goldhammer