Guidance for Industry

Continuous Marketing Applications: Pilot 2 – Scientific Feedback and Interactions During Development of Fast Track Products Under PDUFA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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I. INTRODUCTION

This document is intended to provide guidance to industry on how the Agency will implement a pilot program (Pilot 2) to test the continuous marketing application (CMA) concept during the IND (investigational new drug application) phase of new drug and biological product development.

Pilot 2 provides for frequent scientific feedback and interactions based on a prospectively defined agreement between the FDA and applicants. Pilot 2 pertains only to new drug or biological products that have been designated as Fast Track products pursuant to Section 112 of the FDA Modernization Act of 1997 (Section 506 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 356)[2] and have been selected to participate in the program. The pilot program will be effective from the date that the Notice of Availability for this guidance is published in the *Federal Register* through September 30, 2007, and will include an evaluation component to determine the added value and costs of the program and its impact on the efficiency of the development process. Another pilot program (Pilot 1), to test the CMA concept during the review of new drug applications (NDAs) and biologic licensing applications (BLAs), is the subject of a separate guidance, *Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products Under PDUFA*. Applications that meet the relevant acceptance criteria may be included in both Pilot 1 and Pilot 2. An application included in the Pilots also may be subject to other special development or approval programs (e.g., 21 CFR 314 Subpart H).

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Additional information regarding Fast Track products (i.e., those products intended to treat a serious and/or life-threatening disease for which there is an unmet medical need) and the Fast Track program, including product designation and the program associated with such designation, is available in the FDA guidance *Fast Track Drug Development Programs – Designation, Development and Application Review*.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In conjunction with the June 2002 reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA), the FDA agreed to meet specific performance goals (PDUFA goals). The PDUFA goals are described in *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated June 4, 2002, from the Secretary of Health and Human Services to Congress.[3] The PDUFA goals outline the basic elements of two pilot programs to explore the CMA concept.

The CMA concept builds on the current practice of interaction between the FDA and applicants during drug development and application review and proposes improvements. Under PDUFA, two exploratory pilot programs will be conducted to allow for a comprehensive assessment of the added value, costs, and impact of more extensive feedback during drug development and early review of parts of marketing applications. These pilot programs will provide the Agency with important information regarding whether such activity can improve the efficiency of the drug development and review process and shorten review time.

For many years, the FDA has engaged in early review of parts of marketing applications prior to submission of the entire application. For example, under section 112 of the FDA Modernization Act of 1997, the FDA has conducted for the past several years *rolling reviews* of some presubmitted portions of Fast Track marketing applications on a resource-available basis. Although such Agency activities are believed to improve the efficiency of the drug development and approval process for Fast Track products, no formal program to assess the value, costs, and impact of such activities has been undertaken.

Under the first CMA pilot program, Pilot 1, the subject of a separate guidance, applicants submitting NDAs or BLAs for products designated as Fast Track products may be eligible, based on the terms and conditions agreed upon by the applicant and the FDA, to submit portions of their marketing applications (*reviewable units*) before submitting the complete marketing application. The FDA has agreed to complete reviews of such reviewable units within a specified period of time and to provide early feedback for the presubmissions in the form of

[3] The letter was sent to Congress with identical copies addressed to the Chairman and Ranking Minority Members of the Committee on Health, Education, Labor and Pensions, United States Senate and Committee on Energy and Commerce, United States House of Representatives. The PDUFA Goals can be found at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html.

discipline review letters.[4] Pilot 1 also will evaluate the benefits and costs of providing applicants with such early review feedback.

Under the second CMA pilot program, Pilot 2, the subject of this guidance, the FDA and applicants of eligible Fast Track drug and biological products can enter into an agreement to engage in frequent scientific feedback and interactions during the IND phase of product development. Pilot 2 will evaluate the cost of such enhanced interaction between the FDA and applicants and whether it improves the efficiency and effectiveness of development programs.

III. PILOT 2 IMPLEMENTATION

This section of the guidance describes the application and selection process for participating in Pilot 2 and the process of forming an agreement with the review division on feedback and interactions. This section also outlines the timelines and evaluation process for Pilot 2.

Many requirements for the Pilot 2 program are detailed in the PDUFA goals. The FDA's objective in designing the details of implementation is to maximize the potential public health impact of the resources invested in this exploratory program.

A. Selection of Participant Drug and Biological Products

1. Eligible Drug and Biological Products

Under the PDUFA goals, eligibility for participation in Pilot 2 is limited to drug and biological products that (1) have been designated Fast Track, (2) have been the subject of an end-of-phase 1, or equivalent, meeting, and (3) are not on clinical hold. An equivalent meeting may, in some cases, be a pre-IND meeting for a product that has been previously developed outside of the U.S. The FDA retains the authority to determine whether a pre-IND meeting is adequate to initiate the Pilot 2 process for a particular product.

Pilot 2 will be limited to no more than one Fast Track product for each CDER and CBER review division over the course of the pilot program.[5] The review division and applicant can discuss at the initiation of the IND process the potential for an eligible product to benefit from participation in Pilot 2.

2. Application Process

The selection of products for Pilot 2 will be based on FDA review of a Pilot 2 application. In the Pilot 2 application, the applicant should describe how the Fast Track

[4] The comments included in the discipline review letter are considered preliminary by the FDA and do not represent final Agency conclusions regarding the application. Additional information regarding discipline review letters is available in the FDA guidance *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act*.

[5] Sixteen divisions in CDER and four divisions in CBER will participate in Pilot 2.

product could significantly benefit the public health and how the proposed development program could be significantly enhanced by frequent communications with the FDA.

Each Pilot 2 application should include the following information:

- Cover letter prominently labeled ***Pilot 2 application***
- IND number
- Date of Fast Track designation
- Date of the end-of-phase 1, or equivalent, meeting and summary of the outcome
- A timeline of past and projected milestones from the drug or biological product development program, including projected date of NDA/BLA submission
- Overview of the proposed product development program for a specified disease and indication(s), providing information about each of the review disciplines (e.g., CMC, pharmacology/toxicology, clinical, clinical microbiology, clinical pharmacology, and biopharmaceutics)
- Rationale for participation in Pilot 2, specifying the ways in which development of the subject drug or biological product would be improved by frequent scientific feedback and interactions with the FDA and the potential for such communication to benefit public health by improving the efficiency of the drug development program
- Draft agreement for proposed feedback and interactions with the FDA (see section III.B. below)

Pilot 2 applications should be submitted in triplicate to the attention of the appropriate review division in CDER or CBER as an amendment to the applicant's IND with Form FDA 1571 attached.

3. Criteria for Evaluation and Selection

Pilot 2 applications will be evaluated based on FDA's overall assessment of (1) the potential value of enhanced interaction, emphasizing the potential public health benefit resulting from development of the product, (2) the likelihood that concentrated scientific dialogue will facilitate the availability of a promising novel therapy, and (3) the applicant's demonstration of commitment to product development as evidenced by a thorough consideration of the rationale for participation in Pilot 2.

As noted above, a maximum of one Pilot 2 application for each CDER and CBER review division will be selected to participate in the pilot program. Each selected Pilot 2 product will remain in the pilot program until the program's completion date, unless (1) an NDA or BLA is submitted for the product, (2) the applicant withdraws the product from the pilot program, or (3) the FDA terminates the agreement for the product (see Section B, below). If a Pilot 2 product is withdrawn or terminated from the pilot program *before* the agreement between the review division and applicant is finalized, the review division will replace it with an alternate selection from among the Pilot 2 applications. Pilot 2 products that are withdrawn or terminated from the pilot program *after* an agreement between the FDA and applicant is finalized may be replaced at the discretion of the

division based on the availability of other eligible applications and the remaining duration of Pilot 2.

4. Application Timeline and Applicant Notification

The implementation for Pilot 2 will begin on the date that the Notice of Availability for this guidance is published in the *Federal Register*. Pilot 2 applications will be accepted between that date and December 8, 2003. A single Pilot 2 application for each CDER and CBER review division will be selected from the Pilot 2 applications that are received by December 8, 2003. Those selection decisions will be made by February 9, 2004, and the appropriate FDA review division will notify the applicant of the selected Pilot 2 application in writing. The Agency will inform applicants individually about applications that are not selected.

Divisions that have not received any acceptable Pilot 2 applications by December 8, 2003, will continue to accept applications through September 30, 2004. For each of these divisions, the first application received that meets the evaluation criteria will be accepted into Pilot 2, and the applicant will be informed within 3 months of application submission.

A notice will be made available on the FDA web site to identify the CDER and CBER divisions that have selected a participant application.

B. Agreement on Feedback and Interactions

Once an application is selected for Pilot 2, and prior to engaging in any subsequent Pilot 2 activity, the review division and the applicant will finalize an agreement on the nature of and timelines for feedback and interactions between the applicant and the FDA. The initial basis for this agreement will be the draft agreement submitted by the applicant in the Pilot 2 application. However, the FDA will retain full discretion to determine the contents of the final agreement or to determine that no final agreement can be reached. The final agreement between the review division and the applicant will outline clearly the types of feedback and interactions that are expected to occur along with a tentative timeline. The final agreement will be written to provide reasonable flexibility in implementing and adjusting the agreement as warranted during the drug development program. The final agreement will be shared with the applicant in writing (e.g., in meeting minutes, facsimile, letter). Changes to the agreement can be made by subsequent agreement between the review division and the applicant and should be documented for the record (e.g., in meeting minutes). 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.

The following aspects of interaction between the FDA and the applicant will be addressed as part of the agreement:

- *Frequency of Contact* — This provision in the agreement will outline the timing and/or triggering events that will prompt interaction between the applicant and the FDA review division. The agreement may provide for regular interactions at appropriate times during the development process and/or feedback from the FDA following applicant submission of new information, such as a product development plan, important new protocols, study summaries, or complete study reports.

- *Applicant Submissions* — The applicant and the FDA will agree on the general types of submissions that will stimulate feedback and interactions. Examples include requests for evaluation of proposed preclinical or clinical protocols, product development plans, special protocol assessments, selected study summaries, draft study reports, and final study reports. The Agency expects that study summaries and draft reports, rather than final study reports, will be submitted routinely during the IND process. Applicants should be aware, however, that the FDA cannot anticipate important differences between draft and final study reports. Feedback on development programs will be affected by the quality and completeness of the information available to the FDA at the time of its assessment.

- *Feedback and Interaction from the FDA* — The review division and applicant will agree on the forms of communication (e.g., regular face-to-face meetings, intermittent telephone interactions, written communications, secure e-mail) to use in response to each type of applicant submission. The review division and applicant will also agree on general timelines for responses, providing adequate time for FDA review and anticipating the need of applicants for timely input to their development processes. For submissions subject to PDUFA goals (e.g. requests for special protocol assessment, see FDA guidance *Special Protocol Assessment*), an applicant and review division may negotiate shorter review schedules.

Review divisions will undertake an annual evaluation of each agreement to determine whether the agreement continues to promote the goals of Pilot 2. An agreement may be modified to refine the feedback and interaction process based on applicant needs and other experience with the ongoing program. Certain conditions may require termination of a Pilot 2 agreement and removal of an application from Pilot 2 (e.g., if a development program changes so that it no longer tests the ability of enhanced FDA feedback and interaction with the applicant to promote the development of a highly beneficial product). Such changes in a development program could include failure of an applicant to actively pursue development of the drug or biological product (either with or without termination or withdrawal of the IND), failure of the product to demonstrate a potential ability to meet an important medical need, loss of Fast Track status, 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. Determination of the need to terminate Pilot 2 agreements will be made by the review division in consultation with the appropriate office director.

C. Pilot 2 Evaluation, Reporting, and Conclusion

Pilot 2 agreements and activities for each application will continue through September 30, 2007, the pilot program completion date, unless (1) an NDA\BLA is submitted, (2) the applicant withdraws the product from the pilot program, or (3) the agreement is terminated by the FDA for any of the reasons described above.

An independent, expert consultant will be engaged under a contract with the FDA to evaluate Pilot 2. The consultant will, with input from the FDA, develop an evaluation study design that identifies key questions, data requirements, and a data collection plan, while maintaining applicants confidentiality. The consultant will then conduct a comprehensive study of Pilot 2 to help assess the value, costs, and effects of this program in relation to the product development and review process. Data collection and evaluation is expected to inform and refine the conduct of the program and will begin on the date that the Notice of Availability for this guidance is published in the *Federal Register*.

To evaluate Pilot 2 fully, the independent expert consultant will need access to applicants' feedback. Accordingly, applicants engaged in Pilot 2 will be expected to cooperate with the consultant throughout the program as a mandatory condition for continued participation.

The independent consultant will provide a preliminary report on the evaluation of Pilot 2 to the Commissioner of Food and Drugs by September 30, 2006, with a final report due after September 30, 2007. A version of both the preliminary and final reports, redacted to remove confidential commercial information or other information exempt from disclosure, will be made available to the public. At the conclusion of the pilot program and after review of the preliminary and final reports, the FDA will determine the appropriate plan to handle participating Pilot 2 applications.