Guidance for Industry

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

Draft Guidance

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 45 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) John Jenkins (301-594-3937) or (CBER) Robert A. Yetter (301-827-0373).

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)

June 2003
Procedural

Guidance for Industry

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

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

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)

June 2003
Procedural

TABLE OF CONTENTS

Guidance for Industry[1] Continuous Marketing Applications: Pilot 2 – Scientific Feedback and Interactions During Development of Fast Track Products Under PDUFA

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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) phase of new drug and biological product development.[2]

Pilot 2 provides for frequent scientific feedback and interactions based on a prospectively defined agreement between 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)[3] and have been selected to participate in the program. The pilot program will be effective October 1, 2003, 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. A second pilot program (Pilot 1), to test the CMA concept during the

[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] The Commissioner has announced a consolidation of the CDER/CBER review functions for therapeutic products. Once the consolidation has been completed, we will review those guidances that have been affected by the transfer of functions for possible revision.

[3] 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*.

review of new drug applications (NDAs) and biologic licensing applications (BLAs), is the subject of a separate guidance.

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), 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.[4] 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 FDA and applicants during drug development and application review and proposes ways that improvements can be made. 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, 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, 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 a the terms and conditions agreed upon by the applicant and FDA, to submit portions of their marketing applications (*reviewable units*) in advance of the complete marketing application. FDA has agreed to complete reviews of such reviewable units within a specified timeframe and

[4] 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, House of Representatives. The PDUFA Goals can be found at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html.

to provide early feedback for the presubmissions in the form of discipline review letters.[5] 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, 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 (investigational) phase of product development. Pilot 2 will evaluate the cost of such enhanced interaction between FDA and applicants and whether it improves the efficiency and effectiveness of development programs.

III. PILOT 2 IMPLEMENTATION

This section of the guidance explains how Pilot 2 will be implemented. It describes the application and selection process for participating in the Pilot. It also describes the process of forming an agreement with the review division on feedback and interactions, and it outlines the timelines and evaluation process for Pilot 2.

A. Selection of Participant Drug and Biological Products

1. Eligible Drug and Biological Products

Participation in Pilot 2 is limited to drug and biological products that have been designated Fast Track, and have been the subject of an end-of-phase 1, or equivalent, meeting, and are not on clinical hold. 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. 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 the FDA review of a Pilot 2 application. In the Pilot 2 application, the applicant should describe how their Fast Track product could significantly benefit the public health and how their 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

[5] 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*.

- A timeline of 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 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 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 FDA

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 the potential value of enhanced interaction, emphasizing the potential public health benefit resulting from development of the product, the likelihood that concentrated scientific dialogue will facilitate the availability of a promising novel therapy, and 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). A review division will make an alternate selection from among the Pilot 2 applications to replace any Pilot 2 product that is withdrawn or terminated from the pilot program prior to the finalization of the agreement between the review division and applicant. Pilot 2 products that are withdrawn or terminated from the pilot program after finalization of the agreement will not be replaced.

4. Application Timeline and Applicant Notification

The implementation for Pilot 2 will begin October 1, 2003, if the guidance has been finalized, or later, when the final guidance becomes available. Pilot 2 applications will be accepted between October 1, 2003, and November 30, 2003. Selection of a single Pilot 2 application for each CDER and CBER review division will be made from the Pilot 2 applications that are received by November 30, 2003. A decision on the selected Pilot 2 applications will be made by January 31, 2004, and the appropriate FDA review division will notify the applicant of the selected Pilot 2 application in writing.

However, for divisions that have not received any acceptable Pilot 2 applications by November 30, 2003, applications will continue to be accepted through September 30, 2004. In this case, the first application received that adequately meets the evaluation criteria will be accepted into Pilot 2, and selected applicants will be informed within 3 months of application submission.

All applicants that are not selected will be informed individually.

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 FDA. The initial basis for this agreement will be the draft agreement submitted by the applicant in the Pilot 2 application. However, 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 agreements are to be written in a manner that provides reasonable flexibility in implementing and adjusting the agreement as warranted as the drug development program proceeds. 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 timeframes 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 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 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. 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.

- Feedback and Interaction from 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) that will be expected in response to each type of applicant submission. General timelines for responses will also be agreed on, providing adequate time for FDA review.

Review divisions will undertake periodic re-evaluation of each agreement to determine whether the agreement continues to promote the goals of Pilot 2. Certain conditions may necessitate termination of an agreement (e.g., if a development program changes such that it will no longer test the ability of enhanced 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.

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 an NDA\BLA is submitted, the applicant withdraws the IND for the product, or the agreement is terminated by the FDA, for the reasons described above.

An independent expert consultant will be engaged under a contract with FDA to evaluate Pilot 2. The consultant will have the responsibility, with input from FDA, to develop an evaluation study design that identifies key questions, data requirements, and a data collection plan. The consultant will subsequently 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 will begin October 1, 2003.

To fully evaluate Pilot 2, 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.

A preliminary report on the evaluation of Pilot 2 will be provided by the independent consultant to the Commissioner of Food and Drugs by September 30, 2006, with a final report due after September 30, 2007. A version of the final report, redacted to remove confidential commercial information or other information exempt from disclosure, will be made available to the public.