Guidance for Industry

Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products Under PDUFA

DRAFT GUIDANCE

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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

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 1) to test the continuous marketing application (CMA) concept for the review process for new drug applications (NDAs) and biologic licensing applications (BLAs).[2]

Pilot 1 provides for the review of a limited number of presubmitted portions of an applicant's marketing application (*reviewable units*) based on the terms and conditions agreed upon by the applicant and FDA. Pilot 1 applies only to certain new drug or biological products that have been designated as Fast Track products pursuant to Section 112 of the Food and Drug Administration Modernization Act of 1997 (Section 506 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 356).[3] Pilot 1 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 review process. A second pilot program (Pilot 2), to test the CMA concept for the drug development process, is the subject of a separate guidance.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and 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] Further 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 Drugs 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 opportunities for improvement. 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 activities 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 before the entire application has been submitted. 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 programs has been undertaken.

Under the first CMA pilot program, Pilot 1, the subject of this 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 FDA, to submit portions of their marketing applications (*reviewable units*) in advance of the complete marketing application. FDA has agreed to complete reviews of reviewable units within a specified time and to provide

[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.

early feedback for the presubmissions in the form of discipline review letters.[5] Pilot 1 will also evaluate the benefits and costs of providing applicants with such early feedback.

Under the second CMA pilot program, Pilot 2, the subject of a separate guidance, FDA and applicants with eligible Fast Track drug and biological products may 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 1 IMPLEMENTATION

This section explains how Pilot 1 will be implemented. It defines in detail the process for seeking agreement to participate in this pilot and the meaning of the term *reviewable unit*; it also describes the process for submitting reviewable units and explains how the Agency will be providing early feedback. Finally, the timelines for Pilot 1 and the evaluation process are addressed.

A. Eligible NDA/BLA Applications

Pilot 1 applies to certain drug and biological products that are designated Fast Track drug or biological products pursuant to section 112 of the FDA Modernization Act of 1997 (21 U.S.C. 356). Fast Track products eligible for Pilot 1 will have been the subject of an end-of-phase 2 and/or a pre-NDA or -BLA meeting and will have demonstrated in clinical trials significant promise as a therapeutic advance. Pilot 1 is limited to the initial submission of an NDA or BLA and is not applicable to a resubmission in response to an FDA action letter following the complete review of an NDA or BLA.

Discussion between the applicant and review division of a potentially eligible application for Pilot 1 would occur at the end-of-phase 2 or pre-NDA or -BLA meeting. Discussion can be initiated by the review division or the applicant. Any agreements between the review division and the applicant with regard to participating in Pilot 1 would be finalized before the submission of any reviewable units and would be documented in writing (e.g., in meeting minutes, letter to the applicant). In deciding to accept an application into Pilot 1, the FDA will consider the likelihood that the product will provide an important therapeutic benefit over available therapy for the disease or condition and the likelihood that enrollment in the Pilot will enhance the efficiency of the review. FDA retains the authority to decide whether to accept an NDA or BLA into Pilot 1.

[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. Further information regarding discipline review letters is available in the FDA guidance *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act*.

B. Definition of Reviewable Units

A *reviewable unit* (RU) is a predefined portion of an applicant's NDA or BLA that, by agreement between the applicant and the review division, can be submitted prior to submission of a complete NDA or BLA.[6]

Ideally, an RU would be a complete technical section of the NDA or BLA. Form FDA 356h may be a useful guide to technical sections in a NDA or BLA. Submitting a complete technical section will provide the most comprehensive information and support review efficiency by minimizing the number of times each discipline must engage with the review of a single marketing application. Submitting a complete technical section will also allow FDA to provide a more comprehensive response in the corresponding discipline review letter. However, the experimental nature of Pilot 1 provides for flexibility in the definition of RUs such that a review division and applicant may agree on submission of an RU that is less than a complete technical section (i.e., a well-defined subsection of the complete technical section). Recommendations for potential subsections are provided for each review discipline. Ultimately, the subsections that can be submitted in any incomplete technical section will depend on the content of each NDA or BLA and the anticipated impact of such serial submissions on the efficiency of the review process.

In general, each RU would be similar in quality and completeness to that contained in a complete NDA or BLA submission. Other types of RUs (e.g., submission of draft documents) would be acceptable only in rare cases and with prior agreement of the review division. The applicant should be ready for FDA inspection of the data supporting an RU, consistent with normal procedures applicable at the time of submission of a full NDA or BLA. For example, if the applicant submits an RU for the drug substance, then manufacturing facilities and laboratories associated with the manufacture, packaging, and testing of the drug substance should be ready for FDA inspection.

An RU for a given technical section can consist of any number of the components listed, or other components, based on prior agreement between the review division and the applicant. Where specified in this guidance, the International Conference on Harmonisation (ICH) Common Technical Document (CTD) conventions should be considered and observed in defining RUs. Additional information on the overall format and content of the CTD is available in the FDA guidance *M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use.*

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[6] In accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520), OMB approved the information collection for an application to market a new drug (OMB control number 0910-001, expires March 31, 2005) and to market a biological product (OMB control number 0910-0338, expires March 31, 2005). This guidance merely provides applicants an opportunity to submit already required information in advance of the complete NDA or BLA and contains no new collections of information.

FDA recommendations for subsections that can be considered for potential submission as a reviewable unit are described here for each review discipline.

1. RU for the Chemistry, Manufacturing, and Controls (CMC) Section

Generally, an RU should include the complete CMC technical section for the application. However, with prior agreement of the review division, the following subsections of the CMC complete technical section could be considered an RU. If more than one CMC RU is planned, the sequence of the RU submissions should be specified by agreement. Format and content recommendations are provided in parentheses, referencing the ICH CTD guidance *M4Q: The CTD - Quality.*

Drug Substance Information (Sections 3.2.S.1 through 3.2.S.7 of Module 3) including:

- Relevant information from Overall Quality Summary (Section 2.3 of Module 2)
- Relevant information on Pharmaceutical Development (Section 3.2.P.2.4 of Module 3)
- Appendices (Section 3.2.A of Module 3)
- Regional Information (e.g., for CDER, Methods Validation Section but limited to methods that apply to the drug substance) (Section 3.2.R of Module 3)
- Literature References (Section 3.3 of Module 3)
- Complete stability data package (excluding routine stability updates), as described in the applicable FDA guidances
- Information from the literature and/or from the applicant's own nonclinical and/or clinical studies on impurities qualification

Although FDA understands there may occasionally be a need to accommodate unique circumstances, any CMC submissions subsequent to the drug substance RU(s) are generally expected to be submitted with the complete application. RUs pertaining to the drug product are not encouraged due primarily to the expected increase in review resource utilization.

2. RU for the Nonclinical Pharmacology and Toxicology (P/T) Section

Generally, an RU should include the complete P/T technical section for the application. However, with prior agreement of the review division the following subsections of the P/T complete technical section could be considered an RU. If more than one P/T RU is planned, the sequence of RU submissions should be specified by agreement.

a. Pharmacology studies (including the following as appropriate)

- Pharmacodynamics
- Safety pharmacology
- Pharmacodynamic drug interactions

b. Pharmacokinetic studies (including the following as appropriate)

- Absorption, distribution, metabolism and excretion (ADME)
- Pharmacokinetic drug interactions

c. Toxicology studies (including the following as appropriate)

- Single-dose toxicity
- Repeat-dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Juvenile animal studies
- Local tolerance

3. RU for the Clinical Pharmacology and Biopharmaceutics Section

Generally, an RU should include the complete technical section with four major components (see a through d below): (1) biopharmaceutic studies, (2) studies pertinent to pharmacokinetics (PK) using human biomaterials, (3) human PK studies and (4) human pharmacodynamic studies (PD) including PK/PD studies. The studies in this section are described in the Clinical Summary Section of the ICH CTD M4E — Efficacy (Sections 2.7.1 and 2.7.2). However, with prior agreement of the review division, the following subsections of these major components could be considered an RU. If more than one RU is planned for the clinical pharmacology and biopharmaceutics section, the sequence of RU submissions should be specified by agreement between the applicant and FDA.

a. Biopharmaceutic studies (including, as appropriate)

- Bioavailability (BA)
- Comparative BA and bioequivalence (BE)
- In vitro dissolution
- In vitro/in vivo correlation
- In vitro permeability and solubility
- Bioanalytical and analytical methods for human studies

b. Studies pertinent to PK using human biomaterials

- Plasma protein binding
- Hepatic metabolism and drug interactions
- Studies using other human biomaterials

c. Human PK studies (including, as appropriate)

- Healthy subject PK and initial tolerability
- Patient PK and initial tolerability
- Intrinsic factor PK
- Extrinsic factor PK
- Population pharmacokinetics (PPK)

d. Human PD studies including PK/PD (as appropriate)

- Healthy subject PD and PK/PD
- Patient PD and PK/PD

4. RU for the Clinical Microbiology Section

Generally, an RU for this section should include the complete technical section of the NDA or BLA, unless otherwise agreed to by the review division based on the specific nature of a product development program and content of the associated marketing application.

5. RU for the Clinical Section

Generally, an RU for this section should include the complete technical section of the NDA or BLA, unless another agreement has been reached with the review division based on the specific nature of a product development program and the content of the associated marketing application.

6. Statistical Section

RUs for the CMC, P/T, and clinical sections would usually include statistical analyses, reports, data sets, and related information. Although there may be no specific statistical section RU, there are important statistical issues that will undergo evaluation in each of the other technical sections.

Some of the issues to be addressed in the efficacy and safety submissions are data analysis sets, protocol-specified study designs, statistical data analysis plans, and electronic data formatted as required for a complete submission. Other statistical issues are described in the FDA guidance *E9 Statistical Principles for Clinical Trials*. Potential statistical considerations associated with CMC RU and potential statistical considerations associated with an RU containing P/T carcinogenicity are not discussed in final guidances; however, some discussion of these issues is available in draft guidances.[7]

[7] Draft guidance *(Q1E) Evaluation of Stability Data* and draft guidance *Statistical Aspects of Design, Analysis and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*. Once finalized, these draft guidances will represent FDA's current thinking regarding these topics.

C. Process for Reviewable Units

1. Terms and Conditions for Submission of RU

As already noted, for eligible applications, discussion regarding a plan for RU submissions should be undertaken at the end-of-phase 2 or pre-NDA or -BLA meeting, or at an additional meeting scheduled for this purpose. A plan for RU content and submission sequence should be documented in the meeting minutes or in a separate letter from the review division to the applicant. The documentation should describe the total number of RUs to be submitted for the NDA or BLA, the specific content of each RU, and the projected date for each RU submission.

The documentation should also reference conditions under which the review division will ***not*** review an RU under the terms of Pilot 1 (e.g., if the applicant exceeds the number of agreed-to RUs, submits unacceptable RUs, and/or fails to meet the projected timelines for RU submissions).

For each marketing application, generally no more than one RU should be submitted for review under Pilot 1 for each technical review section. In the event that the initial RU does not constitute a complete technical section for a discipline, the review division may agree to accept an additional presubmission. Generally, the second presubmission accepted for a given discipline would complete the technical section and would generally be reviewed in accordance with the existing presubmission program detailed in the Fast Track guidance. A review division can agree to accept and review more than one RU for a technical section under this pilot program.

Unless otherwise agreed to in advance by the review division, generally no more than four RUs would be accepted and reviewed under Pilot 1 for a single marketing application. This figure includes all RU and presubmissions reviewed under Pilot 1 for all disciplines.

2. Submission and Filing

The submission of RUs for a given application should generally begin no earlier than 1 year in advance of the applicant's anticipated date of submission of the complete NDA or BLA.

Any cover letter for RU submissions should clearly identify the submission as an RU for Pilot 1.

Section 506 (c)(1)(B) of the Federal Food, Drug, and Cosmetic Act requires an applicant to pay fees that may be required under section 736 of the Act before FDA may commence review of any portion of a Fast Track application. The applicant should submit User Fee Form FDA 3397 with any applicable user fee at the time of submission

of the first RU, following the same procedures as those followed when a complete application is submitted.

If, following an initial review (i.e., similar to the *filing review* performed on an NDA or BLA), the review division finds an RU to be substantially complete for review, FDA will start a 6-month review clock for the complete review of the RU of the NDA or BLA. The review clock will start on the date of receipt of the RU (day 0). A decision about whether an RU is substantially complete for review, including whether it meets the terms and conditions of the agency, will be made for each RU within 60 days of receipt (day 60). If an RU is found to be not substantially complete for review, the division will notify the applicant of this finding by letter within 60 days of submission.

An RU may not be accepted if it fails to meet the specifications of the terms and conditions agreed upon by the review division and the applicant, or if the RU is otherwise determined to be incomplete or lacking merit for review.

3. Review Considerations

In general, once an RU is found substantially complete for review by FDA, only minor information amendments submitted in response to FDA inquiries or requests and routine stability and safety updates will be accepted and reviewed during the review cycle.

Major amendments to an RU are strongly discouraged. However, in rare cases and with prior agreement of the review division, FDA may accept and consider for review a major amendment to an RU. To accommodate such rare cases, a major amendment to an RU submitted within the last 3 months of a 6-month review cycle may, at FDA's discretion, trigger a 3-month extension of the review clock for the RU in question.

Any resubmission or amendment to an RU submitted by the applicant in response to an FDA discipline review letter will not be subject to the review timelines of Pilot 1. FDA review of such resubmissions and amendments in advance of submission of the complete NDA or BLA will occur only as resources allow.

Although submission of relevant portions of draft labeling is encouraged to assist with the review division's understanding of the applicant's interpretation of their data, detailed comments on the draft labeling will generally not be provided in a discipline review letter for an RU.

Once accepted for review by FDA, review of an RU will continue and will result in the issuance of a discipline review letter, unless the RU is withdrawn by the applicant or the applicant's participation is terminated by the review division (e.g., due to applicant's failure to fulfill the terms and conditions agreed to by the review division). Review will continue whether or not the complete NDA or BLA is submitted, and any FDA decision about the filing of an NDA or BLA will not ordinarily stop the review clock for ongoing RU submissions.

If the complete NDA or BLA is submitted to FDA while a 6-month review clock for an RU is still open, FDA will adhere to the timelines and performance goals for both the RU and the complete NDA or BLA. For example, if an RU is submitted in January and the complete NDA or BLA is submitted in April, the review goal for the RU will be July and the review goal for the complete NDA or BLA will be either 6 months (October) or 10 months (February), depending on whether the application is designated for priority or standard review. Major amendments to an RU that would extend the review clock for the RU beyond that of the complete NDA or BLA will not be accepted for review unless they meet the criteria for amendments that extend the review clock for the complete NDA/BLA.

4. Discipline Review Letter

After completing an RU review, FDA will provide the applicant written feedback on the review findings in the form of a discipline review letter. One discipline review letter will be issued for each RU, sometimes requiring coordination between disciplines (e.g., clinical and statistical). The discipline review letter will provide preliminary feedback on the individual RU from the discipline review team, rather than definitive decisions relevant to the NDA or BLA from the signatory review division or office. Any labeling comments in the discipline review letter are also considered preliminary and not final Agency comments.

The discipline review letter will be issued consistent with the FDA guidance for industry, *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act* and the PDUFA Goals. In rare instances, the issuance of a discipline review letter may be delayed beyond the PDUFA Goal date pending presentation of the NDA or BLA to an advisory committee. The division will notify the applicant of such a delay and provide an anticipated timeline for issuance of the discipline review letter for the RU.

D. Pilot 1 Timeline and Evaluation

The implementation of Pilot 1 will begin October 1, 2003, if the guidance has been finalized, or later, when the final guidance becomes available. Pilot 1 will continue through September 30, 2007. RUs will be accepted throughout this period.

Data collection and evaluation of Pilot 1, which also will begin on October 1, 2003, will be carried out by an independent expert consultant engaged under a contract with the FDA. 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 assess the value, costs, and effects of this program in relation to the product development and review process.

In order to fully evaluate Pilot 1, the independent expert consultant will need access to applicants' feedback. Accordingly, applicants engaged in Pilot 1 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 1 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.