Guidance for Industry

Continuous Marketing Applications: Pilot 1 – Reviewable Units for 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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Procedural

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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 1) to test the continuous marketing application (CMA) concept for the review process for new drug applications (NDAs) and biologic licensing applications (BLAs).

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 the 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).[2] Pilot 1 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 review process. A second pilot program (Pilot 2), to test the CMA concept for the drug and biological product development process, is the subject of a separate guidance, *Continuous Marketing Applications: Pilot 2 – Scientific Feedback and Interactions During Development of 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 Center for Drug Evaluation and Research (CDER) and 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 Drugs 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 activities 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 portions 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 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 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 reviewable units within a specified period of time

[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.

and to provide early feedback for the presubmissions in the form of 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 a separate guidance, applicants with eligible Fast Track drug and biological products can enter into an agreement with the FDA to engage in frequent scientific feedback and interactions during the IND (investigational new drug application) 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 1 IMPLEMENTATION

This section (1) explains the process for seeking agreement to participate in Pilot 1, (2) defines the term *reviewable unit*, (3) describes the process for submitting reviewable units, and (4) explains how the FDA will provide early feedback. This section also outlines the timelines and evaluation process for Pilot 1.

Many requirements for the Pilot 1 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. Eligible NDA/BLA Applications

Pilot 1 applies to certain drug and biological products that are designated as Fast Track 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. Only the initial submission of an NDA or BLA is eligible for Pilot 1. The program is not applicable to a resubmission in response to an FDA action letter following the complete review of an NDA or BLA. The total number of applications accepted into Pilot 1 will be determined primarily by the number of eligible applications received and the FDA's available resources. Applications not selected for participation in Pilot 1 may be eligible under the Fast Track program for the early submission and review of portions of the application.

The appropriate time for discussion between the applicant and review division of a potentially eligible application for Pilot 1 is at the end-of-phase 2 or pre-NDA or -BLA meeting. The review division or the applicant can initiate discussion. Any agreements between the review division and the applicant with regard to participating in Pilot 1 should be finalized before the submission of any reviewable units and documented in writing (e.g., in meeting minutes, letter to

[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. 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*.

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. In addition, the FDA will consider whether enrollment in Pilot 1, and the investment of resources for early review, may have the potential to enhance the efficiency of the review. Selections will be made by the review division in consultation with the appropriate office director. FDA retains the authority to decide whether to accept an NDA or BLA into Pilot 1.

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.[5]

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 will 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 the 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 from 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

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[5] 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.

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.* The FDA recommends that RUs submitted in electronic format follow the electronic Common Technical Document (eCTD) specifications. Additional information on the eCTD specifications is available in FDA draft guidance.[6]

The FDA's recommendations for subsections that are appropriate as potential RU submissions are described here for each review discipline. These recommendations may be superceded by agreement between the review division and applicant.

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, a subsection of the CMC complete technical section, the drug substance information, could be considered an RU. Other CMC information (e.g., Drug Product Information subsection) may, in rare instances, be accepted as an additional CMC RU with agreement of the review division. If more than one CMC RU is planned, the sequence of the CMC RU submissions should be specified by agreement.

Format and content recommendations are provided in parentheses, referencing the ICH CTD guidance *M4Q: The CTD - Quality.*

In general, an RU containing information on the drug substance should include the following.

- Drug Substance Information (Sections 3.2.S.1 through 3.2.S.7 of Module 3)
- Relevant information from Overall Quality Summary (Section 2.3.S of Module 2)
- Relevant drug substance information in the Pharmaceutical Development Section (Section 3.2.P.2 of Module 2)
- 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

[6] Draft guidance *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions*. Once finalized, this draft guidance will represent FDA's current thinking regarding these topics.

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 section with three major components: (a) pharmacology studies, (b) pharmacokinetic studies, and (c) toxicology studies. However, with prior agreement of the review division, each subsection (a through c) of the complete technical section could be considered an RU. If more than one P/T RU is planned, the sequence of P/T RU submissions should be specified by agreement between the applicant and the FDA.

a. Pharmacology studies (including, as appropriate)

- Pharmacodynamics
- Safety pharmacology
- Pharmacodynamic drug interactions

b. Pharmacokinetic studies (including, as appropriate)

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

c. Toxicology studies (including, 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: (a) biopharmaceutic studies, (b) studies pertinent to pharmacokinetics (PK) using human biomaterials, (c) human PK studies, and (d) 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, each subsection (a through d) of the complete technical section 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 the 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 (including, as appropriate)

- 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 (including, 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 Evaluation

Statistical analyses, reports, data sets, and related information will usually be included in RUs for the CMC, P/T, and clinical sections. Although there may be no specific statistical section RU, important statistical issues 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* and *E10 Choice of Control Group and Related Issues in 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. Some discussion of these issues is available in draft guidances, however.[7]

C. Process for Reviewable Units

1. Terms and Conditions for Submission of RU

As stated, discussion regarding a plan for RU submissions for eligible applications should occur 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 plan for RU submission for each marketing application should generally include no more than one RU submission for review under Pilot 1 per technical review section. However, a review division may agree to a plan that provides for more than one presubmission for any technical review section. The review division will designate in the agreement whether these presubmissions will be considered as RU or non-RU submissions. All RUs submitted for a technical review section would be reviewed sequentially, based on date of receipt, and Pilot 1 timelines would be applicable. Non-RU presubmissions would generally be reviewed in accordance with the existing program detailed in the Fast Track guidance.

Based on FDA resource considerations, generally no more than four RUs would be accepted and reviewed under Pilot 1 for a single marketing application. This figure includes all RUs reviewed under Pilot 1 for all review disciplines**.** In rare cases, the review division may agree in advance to accept more than four RUs.

[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.

2. Submission and Acceptance of RUs

The submission of RUs for an application should generally begin no earlier than 1 year before the date that the applicant anticipates submitting the complete NDA or BLA.

Any cover letter for an RU submission should clearly identify the submission as an RU for Pilot 1 and indicate the relevant review discipline.

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 the 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, the 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).

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. The review division will notify the applicant by letter within 60 days of submission of any RU that is found to be not substantially complete for review. The review division will also provide information regarding the noted deficiencies. The FDA does not intend to accept any RUs after submission of the related complete NDA or BLA.

3. Review Considerations

In general, once an RU is found substantially complete for review by the 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 RU review cycle.

Major amendments to an RU are strongly discouraged. However, in rare cases and with prior agreement of the review division, the 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 final 3 months of a 6-month review cycle may, at the FDA's discretion, trigger a 3-month extension of the review clock for that RU.

Any amendment submitted by the applicant in response to an FDA discipline review letter will not be subject to the review timelines of Pilot 1. The FDA's review of such amendments in advance of submission of the complete NDA or BLA will occur only as resources allow. The cover letter for an amendment submission should identify the number (assigned by the FDA) of the referenced RU.

Although submission of relevant portions of draft labeling is encouraged to assist with the review division's understanding of the applicant's interpretation of the 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 the FDA, review of an RU will continue as currently conducted for complete submissions, including communication with the sponsor for minor clarifications and, if necessary, issuance of information request (IR) letters. The review will result in the issuance of a discipline review letter, unless the applicant withdraws the RU or the review division terminates the applicant's participation (e.g., due to applicant's failure to fulfill the terms and conditions agreed to by the review division). Reviews will continue whether or not the complete NDA or BLA is submitted, and any FDA decision about the filing of an NDA or BLA would not ordinarily stop the review clock for ongoing RU submissions. RU reviews will be completed at the discretion of the review division following withdrawal by the applicant of a complete NDA or BLA.

If the complete NDA or BLA is submitted to the FDA while a 6-month review clock for an RU is still open, the 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 or BLA.

4. Discipline Review Letter

After completing an RU review, the FDA will provide the applicant written feedback on the review findings in the form of a discipline review letter. 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.

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.

In rare instances, the issuance of a discipline review letter may be delayed beyond the PDUFA goal date for the RU 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 Evaluation, Reporting, and Conclusion

The implementation of Pilot 1 will begin on the date that the Notice of Availability for this guidance is published in the *Federal Register* and continue through September 30, 2007. RUs will be accepted throughout this period.

An independent, expert consultant will be engaged under a contract with the FDA to evaluate Pilot 1. 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 observing applicant confidentiality. The consultant will 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 1 fully, the 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.

The independent consultant will provide a preliminary report on the evaluation of Pilot 1 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. In addition, periodic updates will be made available on the FDA web site to provide information on the status of the program (e.g., number of participant applications and RU submissions).