Guidance for Industry

Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act

Comments and suggestions regarding this document should be submitted at anytime 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 title of this guidance document.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
November 2001

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Additional copies of this guidance are available from

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This guidance document represents the agency's current thinking on information request and discipline review letters under the Prescription Drug User Fee Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance for industry explains how the Agency will issue and use information request (IR) letters and discipline review (DR) letters during the review of products in original human drug applications as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g(1)) (PDUFA products). This guidance does not apply to supplemental applications, resubmissions, or to applications for non-PDUFA products.

In a November 1997 letter to Congress regarding the reauthorization of the Prescription Drug User Fee Act (PDUFA) as part of the Food and Drug Administration Modernization Act of 1997, the Secretary of Health and Human Services committed the Food and Drug Administration to certain user fee performance goals and additional procedures related to the review of PDUFA products. These include the goals of reviewing and acting on increasing percentages of applicants' original new drug applications (NDAs) or biologics license applications (BLAs), within 6 months for priority applications and within 10 months for standard applications for drugs and biologics. The term review and act on means the issuance of an action letter after the complete review of a filed application. In addition to the performance goals for application review, to help expedite the development of drugs and biologics, the Secretary specified that FDA intends to provide early Agency thoughts on possible deficiencies to applicants in a letter as each discipline finishes its initial review of its portion of the pending application (except when it results in the ability to issue an action letter).

II. BACKGROUND

Upon implementation of the Prescription Drug User Fee Act of 1992 (PDUFA 1), the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) undertook to review and act on complete NDAs and BLAs within agreed

[1] This guidance has been prepared by the Review Management Working Group comprising individuals in the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

upon time frames. As part of this undertaking FDA instituted the use of two types of letters, action letters and IR letters. FDA issued an action letter (not approvable, approvable or approval letter) after a complete review of the application. If not an approval, the action letter contained a complete list of deficiencies in the application and completed the review cycle for the application. The next review cycle (resubmission) began when the agency receive a complete response to all deficiencies listed in the letter. CDER and CBER used IR letters to ask for information that would assist reviewers during the course of the review or to convey deficiencies identified in the application in advance of the issuance of an action letter. These IR letters did not stop the review clock, did not signal the completion of a review cycle, and were not used consistently across divisions or centers.

In discussions held to prepare for the reauthorization of PDUFA (PDUFA 2), industry proposed that applicants be notified of any deficiencies in an NDA or BLA as early as possible after a discipline review had been completed. It was agreed that deficiencies would be communicated in a specific type of letter. The company could then begin preparing a response to the deficiencies, thereby decreasing the response time to the Agency and potentially expediting availability of products to consumers. Although the enclosure to the PDUFA 2 goals letter signed by Secretary Shalala refers to these as IR letters, FDA finds that it will be less confusing if these letters are clearly identified as a unique type of letter, the DR letter. Consequently the Agency will continue to use an IR letter, if needed, to request information while a specific discipline review is in progress and institute the use of a DR letter to convey early thoughts on possible deficiencies in the discipline's section of the application when a discipline review is complete.

A discipline review refers to the review of sections of the NDA and BLA by staff with that expertise. These sections include, but are not limited to, the clinical section, the chemistry, manufacturing and controls section, the non-clinical pharmacology and toxicology section, and the human pharmacokinetics and bioavailability section. As part of their PDUFA 2 commitments at the conclusion of a discipline review, CBER and CDER will send a discipline review letter to the applicant identifying deficiencies in that particular discipline's portion of an application as described in this document, unless the discipline review completes the review of the application.

III. EXPLANATION OF TERMS

An action letter is a letter to an applicant that is issued after the complete review of a filed application. If the letter is not an approval letter, it will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval. An action letter may contain additional or fewer deficiencies than were provided in previously issued DR letters, depending on the final review of the application and supervisory evaluation by Division and/or Office Directors. The issuance of an action letter completes the review cycle for a pending application. It is the benchmark by which the Agency's performance against the PDUFA application review goals is measured.

A DR letter is a letter used to convey early thoughts on possible deficiencies found by a discipline review team for its portion of the pending application at the conclusion of the

discipline review. FDA does not consider DR letters to be action letters because they do not represent a complete review of the submission and, therefore, do not stop the user fee review clock. In addition, a DR letter does not necessarily reflect input from upper supervisory levels (i.e., Division or Office Directors). A single DR letter may contain comments from multiple discipline reviews if it is more efficient to do so. FDA may review such information if it determines that such review would not adversely affect its ability to meet its PDUFA performance goal for that review cycle. FDA has no obligation to review information submitted in response to a DR letter during the review cycle in which the DR letter was issued.

An IR letter is a letter sent to an applicant during an application review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review. FDA does not consider IR letters to be action letters because they do not represent a complete review of the submission and therefore do not stop the user fee review clock. As with DR letters, an IR letter does not necessarily reflect input from upper supervisory levels. However, IR letters are not like DR letters in that FDA issues IR letters while the discipline review continues. Information requested in IR letters should be information that would assist in the completion of the review and, as such, would usually be reviewed during the review cycle in which the IR letter was issued.

The user fee review clock measures the time elapsed during which an application is under review by CBER or CDER (i.e., a review cycle). The review clock starts at Agency receipt of an NDA or BLA that is subsequently filed, or a complete resubmission and stops when the agency issues an action letter to the applicant.

IV. ISSUANCE AND USE OF INFORMATION REQUEST AND DISCIPLINE REVIEW LETTERS

A. General

CBER and CDER will use IR letters to obtain clarifying information to assist in completing a review. Because the Agency issues IRs to obtain clarification, it is normally expected that the applicant will respond as quickly as possible. FDA reviews such responses (if they are of a clarifying nature) as part of the current review cycle of the application. However, if the response is of a significant nature, the response could constitute a major amendment. Major amendments to an original application received in the last three months of the review cycle may extend the Action Due date by three months. Only one such extension is permitted. FDA may defer the review of a response to the next review cycle, if the review team believes that the new information cannot be fully reviewed in the time remaining in the current review cycle or is ready to issue an action letter.

To help expedite the development of drug and biologic products, under PDUFA 2, CBER and CDER will generally convey early thoughts on possible deficiencies to applicants in the form of a DR letter as each discipline finishes its review of its section of the pending application, unless the discipline review completes the review of the application. FDA will not issue a DR letter if its issuance would delay or coincide with the issuance of an

action letter. You should not construe the absence of a DR letter for a particular discipline to mean that the action letter will not contain any deficiencies for that discipline. Comments in a DR letter will usually reflect the input of the review team but not that of the review division director or office director.

The DR letter will allow applicants to know as soon as possible the review team's early thoughts on possible deficiencies that have been identified within specific sections of the application. With this information they can begin to assemble the needed data to address these deficiencies. DR letters will only contain items that the review team believes require resolution prior to approval of the product. A DR letter intended to convey deficiencies found during a discipline review will be clearly distinguishable from IR letters, which are requests for clarifications needed to proceed with the on-going review.

Applicants should be aware that because the DR letter will originate at the review team level, supervisors may add or delete items in the course of their evaluation, resulting in more or fewer deficiencies in the subsequent action letter. In addition, as reviews from different disciplines are integrated, additional concerns might arise or previously stated concerns may be resolved. Therefore, applicants could spend time gathering information that in the end may not be necessary for responding to the action letter. This possibility was raised during PDUFA 2 discussions with industry representatives, and it was agreed during those discussions that the DR letter program should be evaluated to determine if it truly helps achieve the goal of reducing the time it takes to make products available to the consumer (i.e. if the benefit of early notification of possible deficiencies outweighs the possibility of unnecessary extra work on the part of industry).

B. Applicant Response and Effect on the User Fee Clock

The IR letters and DR letters will not affect the user fee review clock for a given review cycle. The review team will review responses to IR letters and DR letters during the current review cycle at the discretion of the review team. Normally, unless the amount and type of information is substantive or voluminous, FDA will review a clarifying IR letter response during the current review cycle. We may or may not consider a response to a DR letter conveying deficiencies identified in a discipline review of an original application a major amendment, which would extend the review time for the current review cycle. At the Division's discretion, it may review the response if the review can be completed in the current review cycle. The Agency is not obligated to review the response before the issuance of an action letter. If the Agency determines that it cannot review the newly submitted data before the user fee action due date, it may defer review of the response. If the review team is ready to issue an action letter, review of the response could also be deferred. When FDA defer the review of a response it will be reviewed during the next review cycle for the application as part of the complete resubmission if the applicant references such response in the resubmission.

Deficiencies addressed in a response to an IR letter or a DR letter may appear in an action letter if the review of the response has been deferred or if concerns remain after review of

the response. The action letter will include all deficiencies that must be answered in order to place the application in condition for approval.

If the applicant has already submitted a complete response to all of the outstanding deficiencies, the applicant may simply refer to such responses in the complete resubmission that responds to the action letter; further reiteration of previously submitted information is not necessary. However, the applicant should clearly identify in the resubmission all such responses that are required to complete the resubmission as such.