OFFICE OF NEW DRUGS

NDAs and BLAs: Communication to Applicants of Planned Review Timelines

CONTENTS

PURPOSE

- This MAPP establishes procedures for informing applicants of the planned review timeline, including the goal dates for discussion of labeling and postmarketing study requirements (PMRs) and commitments (PMCs), for original new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements submitted to the Center for Drug Evaluation and Research (CDER).

BACKGROUND

- On September 27, 2007, the President signed Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA), which reauthorizes the Prescription Drug User Fee Act of 1992 (PDUFA) in Title I, Prescription Drug User Fee Amendments of 2007 (PDUFA IV). In conjunction with the reauthorization of PDUFA, the Food and Drug Administration (FDA) agreed to meet specific performance goals. These goals are described in *PDUFA Reauthorization Performance Goals and Procedures*.[1] Under the PDUFA IV goals, CDER agreed to develop procedures for review staff to notify applicants of planned review timelines for original NDA and BLA applications and efficacy supplements.

- Title IX, section 901, of FDAAA also creates a new section 505(o) of the act authorizing the FDA to require certain studies and clinical trials for prescription drugs and biological products approved under section 505 of the act or section 351 of the Public Health Service Act. This new authority became effective on March 25, 2008.

[1] See http://www.fda.gov/oc/pdufa4/pdufa4goals.html.

- The guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* highlights transparency in the review process as a fundamental value.[2] Specifically, it stresses the importance of keeping review staff and applicants informed about how a review is progressing. Both parties can then anticipate and plan their next steps and respond to potential problems as they are identified. Good review management practices (GRMPs) also promote increased consistency in review practices across review divisions and FDA centers.

- The GRMPs call for the establishment of major milestones within the review timeline, including dates for communicating proposed labeling comments and PMCs.

REFERENCES

- *PDUFA Reauthorization Performance Goals and Procedures*, Food and Drug Administration Amendments Act of 2007 (http://www.fda.gov/oc/pdufa4/pdufa4goals.html)

- Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (http://www.fda.gov/cder/guidance/index.htm)

DEFINITIONS

- **Amendment.** A type of submission that provides additional information to a pending application or supplemental application.

- **Cross-Discipline Team Leader (CDTL).** The CDTL is the person responsible for overseeing the review of marketing applications. The CDTL works with the discipline team leaders and the regulatory project manager (RPM) to ensure that scientific and regulatory issues are addressed in a timely fashion and with attention to important issues.

- **Major amendment to a pending application.** An amendment to a pending application that contains one or both of the following: 1) a substantial amount of new data or new information not previously submitted to, or reviewed by, the FDA (e.g., a major new clinical safety or efficacy study report, a proposed Risk Evaluation and Mitigation Strategy), or 2) a new analysis or major reanalysis of studies previously submitted to the pending application. A major amendment can be solicited or unsolicited.

  – *Solicited amendment.* An amendment submitted in response to an FDA request.

  – *Unsolicited amendment.* An amendment submitted on the applicant's own initiative.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

- **Minor amendment to a pending application.** Any amendment not meeting the criteria for a major amendment (e.g., providing explanatory information about protocol deviations and their effect on the study results, a manufacturing site clarification, submission of limited amounts of data inadvertently left out of a final study report).

- **Planned review timeline (the timeline).** The planned dates for important review milestones for an application. For the purposes of this MAPP, the milestones to be communicated to the applicant must include, at a minimum, the target dates for transmitting initial labeling comments and PMRs/PMCs.

- **Postmarketing commitment (PMC).** Any written commitment made by an applicant to conduct an investigation after approval of a marketing/licensing application or supplement that is not a PMR.

- **Postmarketing requirement (PMR).** Any study or trial that an applicant is required to conduct after approval of a marketing/licensing application or a supplement. Studies or trials may be required under the Pediatric Research Equity Act (21 CFR 14.55(b) and 601.27(b)), the Animal Rule (21 CFR 314.610(b)(1) and 601.91(b)(1)), Accelerated Approval (21 CFR 314.510 and 601.41), or FDAAA.

- **User fee goal date (PDUFA goal date).** The date by which an action is due on a marketing application under the time frames committed to in goals letters associated with PDUFA.[3]

POLICY

- The original timeline for communication of labeling comments and PMR/PMC requests:

  – Will be consistent with the GRMPs for NDAs and BLAs, taking into consideration the specific circumstances surrounding the individual application.

  – Will be based on the original PDUFA goal date.

  – Will set forth the target date for communication of proposed labeling comments and PMR/PMC requests.

- Major amendments to the application may change the timeline or in certain circumstances cause the timeline to be withdrawn and not reissued. (See the Procedures section for a description of situations in which this may occur.)

- Amendments that are not considered major will not affect the timeline.

- The timeline will be included in the filing communication letter for NDAs and BLAs. Any changes to the timeline, once it is established, will be communicated to the

[3] See note 1, supra.

applicant by letter, telephone conference, facsimile, secure e-mail, or other expedited means.

- No timeline will be communicated for applications that are filed over protest in response to a refuse-to-file decision by the FDA.

RESPONSIBILITIES

Original Timeline Communications

- **The RPM is responsible for:**
  - Proposing timeline target dates for labeling and PMR/PMC communication based on review classification (i.e., priority or standard) of the application.
  - After the filing meeting, communicating the timeline to the applicant in the filing communication letter for NDAs and BLAs.
  - When significant deficiencies preclude discussion of labeling or PMRs/PMCs:
    - Notifying the applicant that significant deficiencies preclude the discussion of labeling or PMRs/PMCs by the target date identified in the timeline.
    - Notifying the applicant of the deficiencies, generally in advance of the target date identified in the timeline.[4]
- **The CDTL is responsible for:**
  - In consultation with the review team, notifying the RPM and division director of the review team's agreement with or modification of the RPM-proposed timeline target dates.
  - Recommending to the division director whether significant deficiencies in the application preclude communication of labeling or PMRs/PMCs by the target date identified in the timeline.
  - Conveying the deficiencies to the RPM for inclusion in the discipline review letters.
- **The Division Director is responsible for:**
  - Approving the target dates for the communication of proposed labeling and PMRs/PMCs at the filing meeting.

[4] See the guidance for industry *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act*.

– In consultation with the review team, determining whether or not significant deficiencies in the application preclude communication of labeling or PMRs/PMCs by the target date identified in the timeline.

Considering and Implementing Potential Changes in the Timeline Resulting From a Major Amendment during the Review Cycle[5]

- **The RPM is responsible for:**

  – In consultation with the CDTL and division director, determining whether an amendment to an application:

    - Is major or minor
    - Is solicited or unsolicited
    - Will be reviewed or not reviewed during the review cycle
    - Does or does not extend the PDUFA goal date
    - Does or does not change the timeline

  – When a major solicited amendment extends the PDUFA goal date:

    - In consultation with the CDTL and division director, determining revised target dates for the communication of labeling comments and PMRs/PMCs.

    - Notifying the applicant that the amendment will be reviewed.

    - Notifying the applicant of the new PDUFA goal date.

    - Notifying the applicant of the new timeline.

  – When a major solicited amendment does not extend the PDUFA goal date but will be reviewed:

    - In consultation with the CDTL and division director, determining whether the original timeline will be retained.

    - Notifying the applicant that the amendment will be reviewed.

    - Notifying the applicant as to whether the original timeline is applicable and, if not, that a new timeline will not be provided.

  – When a major solicited amendment will not be reviewed:

    - Notifying the applicant that the amendment will not be reviewed during this review cycle and that the original timeline still applies.

  – When the division director in consultation with the review team decides to review a major unsolicited amendment:

[5] See Attachment A, Timeline Process for Major Amendments, for an illustration of paths for evaluating original timelines when major amendments are submitted to the application.

- Notifying the applicant that the amendment will be reviewed.
- Notifying the applicant that the original timeline is no longer applicable and that a new timeline will not be provided.
- Notifying the applicant if the PDUFA goal date will be extended.

– When the division director in consultation with the review team decides not to review a major unsolicited amendment:

- Notifying the applicant that the amendment will not be reviewed during this review cycle and that the original timeline is still applicable.

– When significant deficiencies preclude discussion of labeling or PMRs/PMCs:

- Notifying the applicant that significant deficiencies preclude the discussion of labeling or PMRs/PMCs by the target date identified in the timeline.
- Notifying the applicant of the deficiencies, generally in advance of the target date identified in the timeline in a discipline review letter.

- **The CDTL is responsible for:**

– In conjunction with the division director and RPM, determining whether the amendment is major or minor, solicited or unsolicited, will be reviewed or not during the review cycle, and whether or not to extend the PDUFA goal date.

– In conjunction with the division director and review team, determining whether the original timeline will be retained for a major solicited amendment accepted for review within the same PDUFA goal date.

– In conjunction with the division director and review team, establishing a new timeline for a solicited major amendment that extends the PDUFA goal date.

– Recommending to the division director whether significant deficiencies in the application preclude communication of labeling or PMRs/PMCs by the target date identified in the timeline.

- **The Division Director, in consultation with the review team, is responsible for:**

– Determining whether amendments are major or minor, solicited or unsolicited, will be reviewed or not, and whether or not to extend the PDUFA goal date.

– Determining whether the original timeline is still justified based upon the receipt of a solicited major amendment that is accepted for review but that does not extend the application PDUFA goal date.

- Determining whether significant deficiencies in the application preclude communication of labeling or PMRs/PMCs by the target date identified in the timeline.

PROCEDURES

Major Amendments

- Major amendments may be solicited or unsolicited. The review division, in consultation with the review team, decides whether to review a major amendment during the review cycle, whether the goal date can be extended based on the timing of the submission of the amendment and other characteristics of the application, and whether the original timeline still applies. The review division will notify an applicant promptly of its decision regarding review of a major amendment, whether the goal date will be extended, and whether the original timeline is still applicable.

  - **Solicited Amendments**

    - **Accepted for Review**

      1. If the solicited major amendment does not result in an extension of the PDUFA goal date, depending upon the circumstances, the review division may choose to retain the previously communicated timeline (e.g., the amendment is submitted early in the review cycle and its review is not expected to significantly alter the timeline). The review division will notify the applicant that the amendment will be reviewed according to the original timeline.

      2. If the solicited major amendment does not result in an extension of the PDUFA goal date and the review division chooses not to retain the previously communicated timeline (e.g., the amendment is submitted late in the review cycle but not late enough to allow for a goal date extension (i.e., in the last 90 days)), the review division will notify the applicant that the amendment will be reviewed, but that the original timeline no longer applies and no new timeline will be provided.

      3. If the solicited major amendment is submitted during the last 90 days of the review cycle and results in an extension of the PDUFA goal date, the review division will establish a new timeline. The review division will notify the applicant that the amendment will be reviewed and it will provide the new PDUFA goal date and new timeline.

    - **Not Accepted for Review**

      If a solicited major amendment is not accepted for review during the review cycle (i.e., review of the data is not anticipated to change the overall regulatory action), the review division will notify the applicant that the

amendment will not be reviewed and that the original timeline is still applicable.

- **Unsolicited Amendments**

  - **Accepted for Review**

    1. If the unsolicited major amendment does not result in an extension of the PDUFA goal date, the review division will notify the applicant that the amendment will be reviewed, the original timeline is no longer applicable, and a new timeline will not be provided.

    2. If the unsolicited major amendment is submitted during the last 90 days of the review cycle and results in an extension of the PDUFA goal date, the review division will notify the applicant that the amendment will be reviewed and it will provide the new PDUFA goal date. In addition, the review division will notify the applicant that the original timeline is no longer applicable and that a new timeline will not be provided.

  - **Not Accepted for Review**

    If the review division chooses to not review an unsolicited major amendment during the review cycle, it will notify the applicant that the amendment will not be reviewed and that the original timeline is still applicable.

Minor Amendments

- Minor amendments will not affect the timeline.

Deficiencies that Preclude Discussion of Labeling and PMRs/PMCs

- In the event the review division determines that significant deficiencies in the application preclude discussion of labeling or PMRs/PMCs by the target date, the review division will communicate to the applicant no later than the target date, generally through the issuance of a discipline review letter, the deficiencies and its determination that the deficiencies preclude discussion of labeling or PMRs/PMCs. After communicating this decision, the review team may choose to communicate to the applicant any revisions of those labeling sections not affected by the deficiencies.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

Attachment A
Timeline Process for Major Amendments