REVIEW MANAGEMENT

NDAs: PREAPPROVAL SAFETY CONFERENCES

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PURPOSE

To provide a routine, formal mechanism for communication between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to the approval of a new chemical entity (NCD) or certain other applications with the goals of :

1. Ensuring that OPDRA is aware of potential postmarketing safety problems in drugs about to be approved

2. Considering, jointly, the need for any special postmarketing analyses, or postmarketing safety studies, or other evaluations to be implemented by or agreed to by the sponsor prior to the approval of a drug product

3. Determining if there is any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate postlaunch life of the soon-to-be-approved drug product

BACKGROUND

Every new drug marketing application (NDA) contains an integrated analysis of all available information pertinent to the safety of the drug, including animal toxicology data, clinical adverse event data, data on actual or potential drug/drug interactions, data from epidemiologic and other studies of similar compounds, and foreign marketing experience (if any). During the marketing application review period, sponsors are required to submit updates as new data become available.

The review of these safety data and the integrated assessment of both the safety and effectiveness data into an overall risk–benefit conclusion for the product is the primary responsibility of the ODE review division and immediate office. In general, this risk–benefit conclusion applies to the drug when the drug is used as described in the approved labeling.

It is accepted and inevitable that new information about the safety profile of a drug product will emerge once it goes on the market following its launch. The present size of most new drug development programs is such that there is reasonable assurance of detecting at least one event of a particular kind if the frequency of occurrence of the event is in the range of at least 1/500 to 1/1000. Even if an event is serious and easily recognizable as an adverse reaction to the drug, if the frequency is less than 1/1000, it cannot usually be detected reliably during routine new drug development programs.

Because of this reality, CDER uses various postapproval safety surveillance tools to detect unexpected, relatively rare, suspected adverse drug reactions (SADRs). The primary responsibility for postapproval oversight and monitoring resides with OPDRA. The goal is to detect suspected serious reactions as quickly as possible so that the newly detected risk can be communicated promptly and necessary adjustments to labeling or marketing status can be made promptly.

Although unexpected serious SADRs often arise without any previous warning, others represent more severe manifestations of events that occurred during preapproval clinical development or were noted in nonclinical studies submitted in support of the marketing application. Awareness by OPDRA of those events may enable earlier appreciation of the significance of postapproval reports. In some cases, an event may not have been identified premarketing as plausibly drug-related, but later events may reveal that it was. Again, OPDRA awareness of such events prior to approval may lead to earlier appreciation of their significance in the postmarketing setting.

It is important that OPDRA have as much insight as possible into potential safety concerns in the marketing application databases. OPDRA expertise should be tapped when special postapproval safety evaluation is agreed to with the sponsor prior to approval. This requires that a regular, routine communication process exist between OPDRA and the ODE review divisions for the discussion of and risk management planning for potential safety concerns with products about to be released onto the U.S. market. An ad hoc approach to these issues will be less effective and complete.

This MAPP describes the policies and procedures for ensuring communication of safety concerns between the OPDRA risk evaluation divisions and the ODE review divisions before approval of NCEs and certain other marketing applications.

POLICY

Whenever it appears that a marketing application for an NCE is going to be approved, the ODE review division will schedule a preapproval safety conference with the appropriate OPDRA risk evaluation division prior to the approval action. This meeting will generally be held at least 4 weeks prior to the expected product approval day. This meeting may be combined with another planned ODE review division meeting if such is thought to be a better use of time and resources and if such occurs in the general time frames mentioned in this MAPP. The purposes of the preapproval safety conference are several-fold:

- To educate the OPDRA division about the NDA safety database of the new product, especially aspects of the safety database that could be important postapproval, noting, in particular:

    1. Serious events that could prove fatal if more severe

    2. Nonserious events that could have more serious manifestations (e.g., mild hepatic, QT, renal, cardiac, myelosuppressive, or allergic reactions)

    3. Serious events attributed to underlying disease or other treatments that could, nonetheless, be related to the new drug

    4. Limitations of the development database (e.g., exclusions of patients with underlying diseases or other treatments, duration of exposure to the new drug)

    5. Planned or ongoing phase 4 efficacy or other development studies

    6. Any other actual or potential safety concern that deserves OPDRA attention

- To plan and agree on a postapproval safety surveillance strategy for the product, including any commitments CDER would want from the sponsor, for example:
- monitoring for additional cases of serious events not considered drug-related; monitoring for more serious or more severe manifestations of events observed preapproval; monitoring for SADRs observed with other members of the pharmacologic class but not yet observed in the clinical trials of the new product; monitoring for potential drug/drug or drug/food interactions; monitoring for safety concerns in special population subsets, including pregnant women.

- To consider whether particular postmarketing safety studies or other safety evaluation schemes by the sponsor are needed and whether they should be agreed to by the sponsor prior to approval of the product (i.e., noted as postmarketing, P4, or commitments in the approval letter).

- To agree on what types of postapproval feedback the ODE review division would find helpful from the OPDRA risk revaluation division, and the format and timing of such agreed feedback.

- To ensure that the OPDRA division is aware of the planned labeling for the product and to ensure that any OPDRA concerns about potential medication errors relative to labeling have been addressed.

- To provide an opportunity for OPDRA consultative input on qualitative and quantitative consistency of risk communication in proposed labeling.

- To provide an opportunity for OPDRA feedback to the review division on the impact of proposed labeling on expected adverse reaction reporting regulation compliance.

- To determine if OPDRA should grant any waiver or other changes in routine postapproval safety reporting requirements.

The meeting described in the preceding paragraphs must be held for all NCEs unless it is agreed by the ODE review division and the OPDRA division director that such a meeting is unnecessary. Any such agreement should be documented in the NDA file.

If the ODE review division or the OPDRA risk evaluation division believes it would be beneficial for such a meeting to occur for a product that is not an NCE, the meeting will occur upon the request of either division. Typical cases where this might occur would be for new dosage forms or combinations or new uses that would greatly expand use of a particular active moiety or that would present special safety concerns that would require more than routine postapproval surveillance.

Often, having representatives from DDMAC participate in this meeting would be very helpful – both to ensure that DDMAC understands the product=s safety concerns and to ensure that wording chosen to convey such concerns in labeling will not adversely affect DDMAC=s ability to ensure postapproval promotion consistent with the desires of the divisions with regard to safety. The ODE divisions should invite DDMAC representatives to this meeting routinely.

Other formal and informal interactions between OPDRA and ODE review divisions (during the IND, application review, and postapproval phases of a drug) are highly

encouraged when either division believes it has information or access to resources that might help the other.

RESPONSIBILITIES and PROCEDURES:

- The ODE review division project manager responsible for managing the review of a marketing application for an NCE (or other appropriate application) will do the following:

    1. Contact their division=s counterpart OPDRA division and schedule a preapproval safety conference to be held at least 4 weeks (or other time as mutually agreed) prior to the expected day of the application=s approval action.

    2. Ensure that the preapproval safety conference is co-chaired by the review division director and the appropriate OPDRA division director.

    3. Ensure that minutes of the meeting are recorded and distributed within 30 days of the meeting (or as mutually agreed). In any case, they must be part of the final action packet on the product.

    4. Provide copies of the draft or final medical officer review, the draft approval letter, if available, and the draft labeling text to their counterpart OPDRA division at least a week prior to the scheduled meeting, if possible.

    5. Ensure that copies of any complete response letter and any accompanying draft labeling for an NCE is sent to their counterpart division in OPDRA.

- The appropriate OPDRA and ODE division directors will ensure that the appropriate members of their staffs are present for the preapproval safety conference and for other similar meetings scheduled between OPDRA and the ODE review division.

- OPDRA will establish a tracking system for preapproval safety conferences.

EFFECTIVE DATE

This MAPP is effective on the date of publication.