
REVIEW MANAGEMENT

Risk Management Plan Activities in OND and ODS

CONTENTS

PURPOSE

BACKGROUND

DEFINITIONS

POLICY

RESPONSIBILITIES AND PROCEDURES

EFFECTIVE DATE

PURPOSE

- This MAPP documents the procedures for communication and the coordination of work between the staff of the Office of New Drugs (OND), its Offices of Drug Evaluation (ODEs), and the Office of Drug Safety (ODS)¹ in the performance of activities described in the PDUFA Reauthorization Performance Goals and Procedures, Section VIII, Pre- and Peri-NDA/BLA Risk Management Plan Activities (PDUFA Goals),² with the objectives of:
 - Ensuring appropriate participation of staff in internal and external meetings pertaining to risk management plan activities
 - Defining the roles and responsibilities of OND and ODS in the review of documents that pertain to risk management plan activities

¹ The ODS has three divisions: the Division of Drug Risk Evaluation (DDRE); the Division of Surveillance, Research, and Communication Support (DSRCS); and the Division of Medication Errors and Technical Support (DMETS). Other offices within the Center for Drug Evaluation and Research (e.g., Office of Compliance, Office of Regulatory Policy, Office of Generic Drugs) and the Agency (e.g., Office of Chief Counsel) may also have responsibilities during risk management planning and implementation. Although these offices should be consulted as appropriate, this MAPP is intended only to address the policy and procedures specifically related to the interactions between OND and ODS.

² See PDUFA Reauthorization Performance Goals and Procedures (<http://www.fda.gov/cder/pdufa>). “For NDA/BLA applications, and supplements containing clinical data, submitted on or after October 1, 2002, FDA may use user fees to review an applicant’s implementation of the risk management plan for a period of up to two years post-approval for most products and for a period of up to three years for products that require risk management beyond standard labeling (e.g., a black box or bolded warning, medication guide, restricted distribution). This period is defined for purposes of the user fee goals as the peri-approval period. Issues that arise during implementation of the risk management plan (e.g., whether the plan is effective) will be reported to FDA either in the form of a PSUR or in a periodic or annual report (21 CFR 314.80 and 314.81) (ICH Guidance E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs) and addressed during the peri-approval period through discussions between the applicant and FDA. PSURs may be submitted and reviewed semi-annually for the first two or three years post-approval to allow adequate time for implementation of risk management plans.” PDUFA Goals, Section VIII.

BACKGROUND

- The PDUFA Goals include the following performance goals for the Food and Drug Administration (FDA):
 - Review pre-new drug application/biologics license application (pre-NDA/BLA) meeting packages that include summaries of relevant safety information and industry questions/discussion points regarding proposed risk management plan activities and discuss the need for any post-approval risk management studies;
 - Hold discussions during pre-NDA/BLA meetings with industry on preliminary risk management plan activities as warranted;
 - Review proposed risk management plan activities included in an NDA/BLA, if warranted;
 - Review applicants' implementation of risk management plan activities for a period of up to 2 years post-approval for most products and for a period of up to 3 years for products that require risk management beyond standard labeling as reported in the periodic safety report or other regulatory submissions; and
 - Develop guidance documents that address good risk assessment, risk management, and pharmacovigilance practices.
 - The following guidances for industry meet the PDUFA Goals and are available on the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.
 - Guidance for industry *Premarketing Risk Assessment*
 - Guidance for industry *Development and Use of Risk Minimization Action Plans*
 - Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*
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DEFINITIONS

- **Periodic safety reports** include periodic adverse drug experience reports (21 CFR 314.80(c)(2)), periodic adverse experience reports (21 CFR 600.80(c)(2)), and periodic safety update reports (PSURs) (ICH E2C).³
- **Pharmacovigilance plan** is the applicant's observational (nonrandomized) post-approval data-gathering activities relating to the detection and assessment of adverse events that

³ See ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* (<http://www.fda.gov/cder/guidance/index.htm>).

are above and beyond routine postmarketing surveillance. These activities may include expedited reporting of selected adverse events, active surveillance strategies, or the conduct of post-approval observational studies, registries, or surveys.

- **Risk management** is an iterative process of (1) assessing a product's risk-benefit balance; (2) developing and implementing tools to minimize its risks while preserving its benefits; (3) evaluating tool effectiveness and reassessing the risk-benefit balance; and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the risk-benefit balance. Together, risk assessment and risk minimization form what the FDA calls *risk management*.
 - **Risk management plan activities** is the term used in the PDUFA Goals and involves proposed or ongoing activities relating to risk management including the submission and review of pre-NDA/BLA meeting packages and pre-NDA/BLA meetings with industry to discuss safety issues and proposed related activities including Risk Minimization Action Plans (RiskMAPs), post-approval risk management studies, pharmacovigilance plans, and observational studies (e.g., pharmacoepidemiologic studies, registries, and surveys), and the evaluation of the effectiveness of risk minimization action plans.
 - **Risk Minimization Action Plan (RiskMAP)** is a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more *tools* to achieve those goals. See also the guidance for industry *Development and Use of Risk Minimization Action Plans*.
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POLICY

- ODS and OND will provide input to industry on risk management plan activities for the following application categories:
 1. **NMEs/BLAs:** All new drug applications (NDAs) for new molecular entities (NMEs) and all new biologics license applications (BLAs).
 2. **Sponsor Initiated:** Products for which the applicant has questions/discussion points regarding proposed risk management plan activities (may include original NDAs/BLAs and supplements).
 3. **CDER Initiated:** Products not included in the previous categories for which the review division or ODS identifies risk management issues at the time of original NDA/BLA or supplement submission or during the course of the review, including questions/discussion points regarding the need for or review of risk management plan activities (may include original NDAs/BLAs and supplements).

- The OND, through the ODEs and review divisions within OND, has the final decision-making and signatory authority for applications assigned to it.⁴ Differences of opinion are handled through the use of dispute resolution or differing professional opinion procedures (MAPP 4151.1 *Resolution of Disputes: Roles of Reviewers, Supervisors, and Management Documenting Views and Findings and Resolving Differences*; MAPP 4151.2 *Documenting Differing Professional Opinions and Dispute Resolution — Pilot Program*).
 - The OND review division project manager is the Agency point of contact for communication with industry for all issues associated with risk management plans for CDER-regulated products.
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RESPONSIBILITIES AND PROCEDURES

Pre-NDA/BLA

OND

When OND receives a request for a pre-NDA/BLA meeting for an application that requires input on risk management plan activities (NME/BLA, Sponsor Initiated, CDER Initiated), the OND review division responsible for managing the review of the application will do the following:

1. The OND project manager will send a consult to ODS requesting participation in the pre-NDA/BLA meeting. See the specific consult instructions in the CDER Standard Letters (CSL) and Forms Reference Manual under “Consults.”
2. The OND project manager will coordinate with the designated ODS project manager and other appropriate CDER (e.g., Office of Compliance (OC)) or FDA units to coordinate scheduling a pre-meeting and the industry meeting according to established procedures.⁵
3. Within 3 working days of receipt of the meeting package by the OND project manager, the OND project manager will send five copies to the ODS-IO project manager or designee (or, if electronic, the details of the submission location and access), as a follow-up to the previously mentioned consult. The OND project manager will also send an appropriate number of copies to attendees from other CDER/FDA units.
4. OND staff will review the pre-NDA/BLA meeting package to develop comments and to respond to questions/discussion points. The OND project manager will send the

⁴ One exception is the authority to grant waivers of postmarketing safety reporting requirements, as defined in MAPP 6004.1 *Granting Waivers Under 21 CFR 314.90 for Postmarketing Safety Reporting Requirements Under 21 CFR 314.80*. ODS is responsible for granting these waivers.

⁵ See the guidance for industry *Formal Meetings With Sponsors and Applicants for PDUFA Products* (<http://www.fda.gov/cder/guidance/index.htm>).

draft comments and responses to questions/discussion points regarding proposed risk management plan activities to the ODS-IO project manager or designee for discussion at the pre-meeting. The OND draft comments will be provided to ODS as quickly as OND resources allow, but at least 1 business day before the pre-meeting.

5. At the pre-NDA/BLA meeting, OND staff should ask the sponsor to clearly designate, when the application is submitted, the parts of the NDA/BLA that include proposed risk minimization plan activities. In addition, the FDA may offer suggestions to the sponsor regarding the format and submission of the application that would enable the Agency to most efficiently review the designated sections.⁶

ODS

In response to the request for consultation, ODS will do the following:

1. The ODS-IO project manager or designee will interact with the three ODS divisions and Immediate Office to determine appropriate staff for the review team. The ODS-IO project manager or designee will forward appropriate information and documents to DDRE, DMETS, and/or DSRCS as needed and will inform the OND review division project manager of the ODS staff who should be included in the pre-NDA/BLA meeting with the sponsor and the internal pre-meeting. After the pre-NDA/BLA meeting, the ODS-IO project manager or designee will ensure relevant information is communicated to all three ODS divisions as needed.
2. The ODS-IO project manager or designee will coordinate scheduling of the pre-meeting and pre-NDA/BLA meeting with the OND review division project manager so that key ODS representatives or their designees can attend.
3. The ODS-IO project manager or designee will coordinate participation of appropriate ODS staff at the meetings. The directors or deputies from the ODS-IO or component divisions will be invited to attend these meetings, as needed.
4. ODS staff will review the pre-NDA/BLA meeting package to develop comments and to respond to questions/discussion points. The ODS-IO project manager or designee will send the ODS draft comments and responses to questions/discussion points regarding proposed risk management plan activities to the OND review division project manager for discussion at the pre-meeting. The ODS draft comments will be provided to the OND review division as quickly as available ODS resources allow, but at least 1 business day before the pre-meeting.

⁶ Documents that the FDA may offer suggestions about include:

- Summary and Application (21 CFR 314.50(c))
- Summary and Updates of Safety Information, including the integrated summary of safety and safety update reports (21 CFR 314.50(d)(5)(vi))
- Integrated Summary of the Benefits and Risks (21 CFR 301.50(d)(5)(viii))
- Other documents pertaining to risk management tools and plans

NDA/BLA ReviewReview of Proposed Risk Minimization Plan Activities Included in an NDA/BLA*OND*

1. When an NDA/BLA (or supplement) of the type previously described is submitted in paper form, the OND review division project manager will send five official copies (obtained from the sponsor) of the documents pertaining to the risk management plan activities to the ODS-IO project manager or designee. When an electronic application is received, the OND review division project manager will inform the ODS-IO project manager or designee of the details of the location and access of the submission. These will be accompanied by a consult to ODS for the review of the relevant materials. See the specific consult instructions in CSL under “Consults.”
2. During the review of an NDA/BLA or supplement that was not initially sent to ODS as a consult, if questions/concerns arise regarding the need for or review of a RiskMAP, the OND review division project manager will send five copies (or information on the electronic submission) of the documents describing reasons why a RiskMAP may be needed and the proposed RiskMAP (if available) to the ODS-IO project manager or designee and a consult to ODS. See the specific instructions in CSL under “Consults.”
3. The OND review division project manager will invite the ODS-IO project manager or designee to review team meetings for these applications as appropriate. The ODS-IO project manager or designee will notify the OND project manager of the members of the ODS review team who will attend team meetings.
4. The OND project manager will arrange for a Preapproval Safety Conference or another mutually acceptable meeting regarding these applications. As a part of this meeting, OND will work with ODS to establish a schedule, to begin after product launch, for when ODS reviewers will periodically evaluate postmarketing safety information, including spontaneous adverse event reports, and findings from completed observational studies, registries, and surveys, and present their findings to responsible review division staff.

ODS

1. When the ODS-IO project manager or designee receives a consult that includes a risk management plan related to or concerning multiple divisions within ODS, the ODS-IO project manager will send a copy promptly to the appropriate divisions for review and determination of the ODS project team. The ODS-IO project manager or designee will notify the review division project manager of the membership of the ODS project team and the ODS-IO project manager or designee to contact for the overall consult or for specific components of the risk management plan activity. These activities may fall within the DDRE, DSRCS, and/or DMETS components of ODS.
2. Representatives from the ODS divisions and the ODS-IO will meet routinely to discuss the risk management plan. When comments on or a written review of the risk

management plan are to be provided to OND, the ODS-IO project manager or designee will ensure that it is done by an agreed-upon date.

3. When attending the Preapproval Safety Conference or alternative mutually acceptable meeting, ODS will work with OND to establish a schedule, to begin after product launch, that describes when ODS reviewers will periodically evaluate postmarketing safety information, including spontaneous adverse event reports, drug use, observational studies, registries, and surveys, and present their findings to responsible review division staff.

Peri-Approval Activities

Review of Applicants' Implementation of Risk Management Plan Activities for 2 to 3 Years Post-Approval as Reported in the Periodic Safety Report or Other Regulatory Submissions

OND

1. OND will work closely with ODS and the OC to identify and evaluate issues that will arise during implementation of the risk management plan (e.g., how to evaluate whether the RiskMAP is effective).
2. OND will work closely with ODS and OC to continue to refine risk management plan activities and evaluate the effectiveness of RiskMAPs using outcome and performance measures, such as adverse events or adherence to processes to prevent them (e.g., registration, certification, distribution of educational materials).
3. OND will forward the appropriate information pertaining to changes to RiskMAPs and other risk management plan activities to the ODS-IO project manager or designee.
4. The OND review division project manager will coordinate with the ODS-IO project manager or designee and other appropriate CDER or FDA units to set up pre-meetings with OND and ODS, and/or meetings with ODS, OND, and industry, as appropriate, to discuss issues relating to a RiskMAP and/or other risk management plan activities during the peri-approval period and at other times, as needed.
5. OND will be responsible for scheduling any meetings with applicants to discuss risk management plan activities, and for sending letters to applicants requesting changes to risk management plans.
6. Under current policy, OND has the primary responsibility for the review of periodic safety reports and other regulatory submissions. Exceptions include the review of 15-day alert reports, direct reports of adverse drug experiences, and the authority to grant waivers of postmarketing safety reporting requirements, which are primarily the responsibility of ODS. OND reviewers will evaluate periodic safety reports and present their findings to responsible ODS staff in accordance with the schedule established at the time of approval (see NDA/BLA Review, OND item #4 and ODS item #3).

ODS

1. ODS will work closely with OND to identify and evaluate issues that arise during implementation of the risk management plan activity (e.g., whether the RiskMAP is effective).
2. ODS will work closely with OND and OC to continue to refine risk management plan activities and evaluate the effectiveness of RiskMAPs using outcome and performance measures such as adverse events or adherence to processes to prevent them (e.g., registration, certification, distribution of educational materials).
3. The designated ODS project manager will work with the OND review division project manager to schedule pre-meetings with OND and ODS, and meetings with ODS, OND, and industry to discuss issues relating to RiskMAPs and other risk management plan activities, during the peri-approval period and as needed at other times.
4. ODS will review post-approval safety information, including spontaneous adverse event reports, drug use, and findings from completed observational studies, registries, and surveys, as defined at the Preapproval Safety Conference or other mutually acceptable meeting or as warranted by the receipt of new information. ODS reviewers will evaluate postmarketing safety information and present their findings to responsible OND review division staff according to the schedule established at the time of approval (see NDA/BLA Review, OND item #4 and ODS item #3).
5. Copies of periodic safety reports are forwarded to DDRE after the contractor responsible for AERS data entry and tracking has removed the 3500As (mandatory MedWatch form used by industry) for coding. DDRE staff will review these reports, but the primary responsibility for their review rests with OND. Other regulatory submissions relating to the RiskMAPs and other risk management plan activities will be forwarded and as necessary consulted to the ODS-IO project manager or designee to triage for review. As with periodic safety reports, the primary responsibility for their review is with OND.

EFFECTIVE DATE

This MAPP is effective upon date of publication.