
POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Drug Safety Oversight Board

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PURPOSE

This MAPP describes the organizational structure, roles, and responsibilities of the Drug Safety Oversight Board (DSB) and its staff in the Center for Drug Evaluation and Research (CDER).

BACKGROUND

- The DSB was created in 2005 to provide oversight for the management of drug safety issues in the Food and Drug Administration (FDA) and to provide a forum for internal deliberations on complex safety issues. In addition, the Food and Drug Administration Amendments Act of 2007 (FDAAA) established the DSB with specific responsibility to review disputes regarding Risk Evaluation and Mitigation Strategies (REMS).
- Questions concerning matters of internal policy, such as collaboration among Agency components and federal partners, to enhance drug safety management, are addressed in DSB meetings.
- The DSB acts as an internal management council providing advice to the Director, CDER (Center Director).

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- The DSB is not a federal advisory committee (under 21 CFR 14.1(b)(4)) and does not function as a federal advisory committee (see appended table regarding the different forums available for discussing safety and regulatory issues). Issues that would benefit from advisory committee consultation, such as interpretations of clinical trial data in making drug regulatory decisions, should be taken to the relevant FDA advisory committee, and will not be addressed in DSB meetings.
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POLICY

The DSB is a multidisciplinary, cross-organizational group of government experts established to provide broad scientific and regulatory recommendations on drug safety and communication issues and policies to the Center Director.

The DSB discusses potentially significant drug risks and safety issues that have broad policy implications or that would benefit from wider input than can be provided by internal discussions within CDER. These include:

- Selected emerging or ongoing drug-specific safety and risk management issues
- Effective communication of drug safety information to healthcare professionals, patients, and the general public, when consultation and feedback is requested by the Center Director or the Director, CDER Office of Communications
- Establishment of general policies regarding drug safety issues and approaches to resolving internal policy differences
- Drug safety issues on which there is substantial internal disagreement
- Disputes between a sponsor and CDER concerning a Risk Evaluation and Mitigation Strategy (REMS) that occurs after approval of a prescription product if the sponsor requests DSB review (see “Referrals to the DSB from Sponsors” below)
- Other issues, as deemed appropriate by the Center Director.

The referral of a REMS dispute to the DSB does not preclude use of other venues for discussing and resolving these disputes. Additional efforts to resolve the dispute may be pursued.

RESPONSIBILITIES

The DSB Chairperson will:

- Chair meetings of the DSB

- Advise the DSB Executive Director and staff in the development of the DSB agendas, discussion questions, and follow-up activities
- Communicate with the CDER Director regarding DSB deliberations and recommendations

The Executive Director will:

- Arrange monthly meetings, including ensuring that the meetings proceed according to the agenda's scheduled time allotments
- Facilitate bringing issues before the DSB as described under Procedures below, with a view toward maximizing the active participation of the Board's members during the meeting
- Oversee the scheduling of the DSB discussion of any dispute regarding a postmarket REMS to ensure that statutory timelines are met
- Supervise the DSB staff in activities listed for staff below
- Serve as the primary point of contact for coordinating and responding to inquiries related to the activities of the Board

The DSB members will:

- Prepare for and actively participate in meetings, attend the entire meeting, if possible, and ensure representation by alternate members if necessary
- Identify issues for DSB consideration
- Provide CDER staff resources when needed and as appropriate to work on issues identified by the DSB
- Commit to attendance and to the mission of the DSB

The DSB Staff will:

- Support the DSB Executive Director in duties below, and as assigned
- Maintain a set of upcoming issues in need of discussion by the DSB
- Prepare public summaries, internal minutes, and communications about the DSB for the Center Director and the DSB members
- Schedule meetings and secure meeting sites
- Develop (or assemble) and circulate materials to members, so that members can effectively educate themselves before meetings and spend meeting time in active participation
- Maintain files of DSB activities

- Work with CDER staff to identify emerging safety issues
 - Conduct outreach activities
 - Provide project management and staff support for designated CDER activities in support of FDA's drug safety initiatives and other projects, as needed
 - Keep the DSB Executive Director fully informed of progress and problems, and collaborate with team members to ensure seamless backup for services to the DSB and to senior CDER management
 - Keep the DSB informed of Drug Safety Communications that have been posted or are in preparation
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PROCEDURES

Referrals to the DSB from CDER

- Any organizational unit or individual in CDER may refer a drug safety issue to the DSB for assessment by submitting a request to the Executive Director at DrugSafetyOversightBoard@fda.hhs.gov.

Attendance at and Conduct of Meeting

- DSB meetings are attended by DSB members and are open to CDER staff that has a role in the issues to be discussed and wish to participate in and hear the DSB discussion and deliberations. The DSB staff routinely contacts these members of CDER staff in advance of DSB meetings to invite them to attend and participate.
- The Director and Deputy Directors of CDER may attend DSB meetings to hear discussion and respond to advice previously conveyed by the DSB.
- If a meeting is called to order with a quorum, but attendance later falls below that level either in total number or composition, then the minutes shall reflect the point at which the quorum was lost. From that point, no recommendations may be developed, so the official meeting must end.
- Deliberations are generally internal matters and are not public.
- A meeting summary will be drafted and circulated to the attending members, then finalized and forwarded to the Center Director with a transmittal memo from the Chair through the Executive Director (in the case of REMS disputes, see section below on "Referrals to the DSB from Sponsors").

Decision-making

- Recommendations made by the DSB will be conveyed to the Center Director.

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- Recommendations can be formulated through consensus or by vote.
 - The transmittal memo will briefly highlight any recommendations or advisory comments for which a decision by the Center Director may be needed. Decisions and actions on such recommendations, and other advice, if any, are the prerogative of the Center Director.
 - Decisions made by the Center Director based on recommendations made by the DSB will be implemented through the appropriate program office. DSB oversight does not substitute for management at any organizational level. The Center Director retains final authority for Center decisions. All recommendations of the DSB may be appealed to the Center Director by a dissenting Office Director before the Center Director makes a final decision (procedures for REMS disputes are described below).
 - When subcommittees or working groups are used to consider a new REMS or changes to an existing REMS, meeting summaries of those discussions will be archived in FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) within the application (NDA, ANDA, or BLA) discussed.

Referrals to the DSB from Sponsors

- A sponsor may request a DSB review of a dispute about a REMS occurring after approval of a prescription product approved under a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologic License Application (BLA) by submitting a written request 15 to 35 business days after a dispute between the sponsor and the FDA has been identified. Such a request may be submitted to the DSB mailbox at DrugSafetyOversightBoard@fda.hhs.gov. A sponsor may not request DSB review if the dispute about the REMS strategy is submitted in the application for initial approval of the drug. The sponsor must use the major dispute resolution procedures described in section 101(c) of the Food and Drug Administration Amendments Act of 2007 for such disputes.
- Upon receiving a sponsor's written request, the Executive Director will schedule the dispute for review at one of the next two regular DSB meetings. If that is not possible, a special meeting will be arranged.
- Within five business days after scheduling the review, the Executive Director will post notice on FDA's public internet site that the dispute will be reviewed by the DSB.
- At the meeting time reserved for hearing the dispute, the DSB will hear from both parties, orally and/or in writing, and will review the dispute.
- The portion of the meeting in which the dispute is heard and discussed will be recorded, transcribed, and, after redaction according to disclosure laws and regulation, will be made public within 90 days of the meeting.

- The DSB's recommendation for resolving the dispute will be forwarded to the Center Director no later than five business days after the meeting.
- The Center Director will make the DSB recommendation public no later than five business days after receiving it.
- The Center Director will issue an action letter resolving the dispute no later than seven business days after receiving the DSB's recommendation. At that time, the Center Director will also publicly issue an order resolving the dispute.

Conflict of Interest

- FDA employees with conflicts of interest related to a matter on the agenda will recuse themselves from that portion of the discussion and subsequent voting.
- All non-FDA members are self-screened prior to each meeting for conflicts of interest related to the matters before the DSB. Members with conflicts of interest will recuse themselves from the discussion of matters that form the basis for the conflict.
- The results of conflict of interest screening are noted in the meeting minutes.
- A Drug Safety Board member who has conducted the primary review of the data or served as a deciding official for a regulatory action under consideration should inform the DSB of his or her experience at the opening of discussions of the particular matter. Such members may participate in the DSB discussions. For additional disqualification criteria in the case of REMS disputes, see section 505-1(h)(5)(J) of the Act (21 U.S.C. 355-1(h)(5)(J)).

Additional Information

- Elements that distinguish the role of the DSB from the function of a Regulatory Briefing, Advisory Committee meeting, or the role of the Ombudsman are summarized in Table 1.
- The DSB receives administrative staff support from employees under the leadership of the Executive Director of the DSB.
- After each meeting, a public summary of the topics discussed will be posted on CDER's Web site:
<http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm082136.htm>

REFERENCES

1. FDA, 2007, Food and Drug Administration Amendments Act (FDAAA), Title IX, section 901, sections 505-1(h)(4) and (5); (21 USC 355-1(h)(4) and (5)).

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2. U.S. Code, Title 18, Chapter 11, Sec. 202, Definitions.
 3. HHS, 2010, Regulations 45 CFR 73.735-801, Participation in Matters Affecting a Personal Financial Interest.
 4. HHS, 2007. 45 CFR 73.735-501, Prohibited Acceptance of Gifts, Entertainment and Favors
 5. FDA, 2007, Guidance: Drug Safety Information- FDA's Communication to the Public.
 6. FDA, 2010. Center for Drug Evaluation and Research, MAPP 4151.2 Rev. 1, Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.
 7. FDA, 2010, Regulations 21 CFR 14, Public Hearing Before a Public Advisory Committee.
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DEFINITIONS

Conflict of Interest: Refers to financial ties between government employees and private industry as described in 45 CFR 73.735-501. DSB members may not participate in official matters in which the outcome would have a direct and predictable effect on his or her financial interest.

Emerging Drug Safety Issue: An early signal concerning a potentially significant drug safety concern emerging from postmarket data such as reports of serious adverse drug experiences, clinical trials, clinical pharmacology studies, epidemiological studies, or the scientific literature. Such a signal may relate to new risks or new information about known risks of the drug. This can occur when:

- Early information has become available to FDA about a possible adverse effect of a drug.
- FDA is seeking further information and analyzing the available information.
- If confirmed, the information would be considered an important drug safety issue.

Drug Safety Issue: A drug safety issue that has the potential to alter the benefit/risk analysis for a drug in such a way as to affect decisions about prescribing or taking the drug.

Quorum: The minimum number and composition of members who must be present either to start a DSB meeting or to hold a vote during a DSB meeting. For a quorum to exist, all of the following members must be participate in the meeting:

- The Chairperson, or the Executive Director, or a designated substitute
- Two-thirds of current primary members from FDA, including at least two members each from OSE and OND
- Two members or alternates from outside the FDA

Sponsor: The drug or pharmaceutical company presenting a new drug/biologic application for FDA review.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/4/05	Initial	n/a
3/2/07	1	Added a Background section, added a “Scope of the MAPP” section.
7/8/10	2	Added an attachment, deleted “Scope of the MAPP section”, minor edits throughout.
5/5/14	3	Employed updated template. Added information about subcommittees or working groups. Updated language regarding Drug Safety Communications; added Health Resources and Services Administration and Bureau of Prisons as non FDA members. Other minor edits and corrections.
9/14/16	4	Updated information and designations for membership, other minor edits throughout.

ATTACHMENT 1: Organization**Membership - General**

When vacancies arise, the Center Director will request, through the DSB staff, nominations for members (and alternates) from the directors of each organization represented on the DSB and will then appoint members. There will be equal representation from the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). Members will serve a minimum two-year term. All members except the Chair and Executive Director may vote unless they have recused themselves on a particular matter. As currently configured, the DSB includes a broad and balanced selection of representatives from various CDER organizations, as well as from outside the Center and outside FDA. If CDER's organizational structure changes, the membership may be modified in the future. At the time of issuing this MAPP, the DSB membership was as follows:

Chair:

The Deputy Director for Regulatory Programs of CDER is the non-voting chairperson of the DSB.

Permanent DSB members include:

- Director, Professional Affairs and Stakeholder Engagement, Office of the CDER Director
- Director or designee of the OND
- Director or designee of the OSE
- Director or designee of the Office of Translational Science (OTS)
- CDER Deputy Director for Clinical Science

Rotating Members include:

1. Two representatives and a minimum of two alternates from each of the following Center organizations:
 - OSE
 - OND (to include one member each from the Office of Nonprescription Products and from another OND Division)
 - OTS (to include one member each from the Office of Biostatistics and the Office of Clinical Pharmacology)
2. One representative and a minimum of one alternate from each of the following Center organizations:
 - Office of Compliance (OC)
 - Office of Medical Policy (OMP)
 - Counter-Terrorism and Emergency Coordination Staff (CTECS)

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- Office of Pharmaceutical Quality (OPQ)
 - Office of Generic Drugs (OGD)
3. One representative and a minimum of one alternate from each of the following non-CDER organizations:
 - Center for Biologics Evaluation and Research (CBER)
 - Center for Devices and Radiological Health (CDRH)
 4. A minimum of six representatives and six alternates from other federal healthcare and public health agencies:
 - Non-FDA DHHS affiliates (e.g., Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, Indian Health Service, National Institutes of Health, the Health Resources and Services Administration)
 - Other federal agencies or departments providing healthcare (e.g., Department of Defense, Department of Veterans Affairs, or the Bureau of Prisons)

Consultants

When it is deemed necessary, the DSB may engage special government employees (SGEs) as consultants, as defined in 18 U.S.C. 202(a). Other external scientific experts and consumer and patient representatives may present their views regarding issues before the Board. The Office of Health and Constituent Affairs in the Office of the Commissioner may identify and engage consumer/patient consultants to provide consultation to the DSB, as needed.

Executive Director

See responsibilities section on page 3.

Subcommittees and Working Groups

- The DSB may form subcommittees or working groups to review scientific issues, make recommendations, and implement activities related to the function of the DSB. Chairs, co-chairs, and members of subcommittees and working groups need not be members of the DSB.
- When possible, the DSB will draw upon existing CDER and FDA working groups and committees and coordinate when their work affects ongoing activities.
- A DSB subcommittee may be formed to provide advice to FDA when FDA is considering a new REMS or changes to an existing REMS.

ATTACHMENT 2: CDER Forums for Addressing Complex Safety and Regulatory Issues

Dimension	Regulatory Briefing	Drug Safety Oversight Board	Advisory Committee	CDER Ombudsman
<i>Scope and Purpose</i>	To get advice from CDER leadership on pending difficult regulatory decisions. Attendance is broader than for DSB.	To provide advice to CDER Director and staff on: <ul style="list-style-type: none"> • Management of important drug safety issues • Adjudication of internal organizational disputes regarding a drug safety issue • Development of drug safety management policies • Communicating about emerging drug risks 	To get advice from outside experts on pending regulatory action or general scientific matter	Receives complaints, investigates and acts upon them. Mediates disputes, including differences of professional opinion between individual CDER staff
<i>Audience and Notice of meeting</i>	<ul style="list-style-type: none"> • Internal--CDER staff • Agenda and materials provided ahead 	<ul style="list-style-type: none"> • CDER Director • Internal—CDER staff are invited on a need to know basis • Meeting notice and materials to members and invitees only 	<ul style="list-style-type: none"> • The public, CDER regulators • Notice of meeting published in the Federal Register 	<ul style="list-style-type: none"> • Internal—CDER staff • No meeting notice (see below)
<i>Attributes</i>	<ul style="list-style-type: none"> • Can be set up quickly • Provides review of evidence • Broad CDER participation with internal transparency • Share issues and educate CDER leadership and staff • Generally one-time with no follow up 	<ul style="list-style-type: none"> • Internal deliberations • Broad membership (FDA and other Federal Agencies) • Staff designated to provide support • Freedom to set own agenda 	<ul style="list-style-type: none"> • External transparency • Formal process • Variety of committees/expertise • Issues are about 2/3 pre-marketing and 1/3 post-marketing, in addition to large general matter issues • FDA background information made available to public (with redaction) 	<ul style="list-style-type: none"> • Likely to be confidential, depending on the nature of the dispute or issue.

MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH

MAPP 4151.3 Rev. 4

Dimension	Regulatory Briefing	Drug Safety Oversight Board	Advisory Committee	CDER Ombudsman
<i>When to Use</i>	<ul style="list-style-type: none"> • Focus on single drug or class • Need for timely feedback 	<ul style="list-style-type: none"> • Emerging safety issue, prior to clear regulatory pathway • Broad range of safety and safety communication issues • Deal with difficult issues that cross multiple offices • Provide advice on issues that raise policy questions and/or concerns 	<ul style="list-style-type: none"> • High profile, controversial issues (both product or drug class specific and general matter issues) • Close decision calls • Novel drugs • Need for outside expertise and public input 	<ul style="list-style-type: none"> • Dispute between FDA and product sponsor • Part of the process for resolving individual differences of professional opinion