
POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: OND Review Management of INDs and Marketing Applications for Nonprescription Drug Products

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PURPOSE

- This MAPP establishes Office of New Drugs (OND) policies and procedures for the regulatory management and review of investigational new drug applications (INDs) and marketing applications (e.g., new drug applications (NDAs) and supplemental applications (sNDAs)) for nonprescription drug products.
- This MAPP is one in a series of MAPPs designed to document good review practices (GRPs) for review staff in accordance with MAPP 6025.1 *Good Review Practices*. General policies, responsibilities, and procedures regarding all GRPs are contained in MAPP 6025.1 and apply to this MAPP.

BACKGROUND

- The Division of Nonprescription Drug Products (DNDDP) in OND is responsible for the development, oversight, and regulation of nonprescription drug products. In addition, one or more OND divisions provide therapeutic expertise in the review of submissions for drug products intended for over-the-counter (OTC) marketing.

POLICY

- DNDP will manage INDs, NDAs, and NDA supplements (sNDAs) for all nonprescription drug products, including prescription (Rx)-to-OTC switches.
- DNDP will request a review (e.g., collaborative or consultative) for scientific advice as needed from OND and other Center for Drug Evaluation and Research offices.
- DNDP will sign the action letters for all NDAs and sNDAs for nonprescription drug products except those applications that represent first-in-class nonprescription drug products. Actions on first-in-class nonprescription drug product NDAs will require dual sign-off by Office of Drug Evaluation (ODE) IV and the corresponding ODE with regulatory oversight of the relevant class of prescription drug products or indication(s), unless otherwise stated (see below).

RESPONSIBILITIES

- DNDP will establish the review teams responsible for the review of INDs, NDAs, and sNDAs. DNDP will include appropriate members from DNDP and the specific subject matter review division (SSMRD) on each review team.
- DNDP will manage meetings and facilitate active participation on the IND and NDA/sNDA review teams by appropriate staff from both DNDP and the SSMRD.
- Each review team will decide which members will review the various sections of an application, consistent with the general review procedures described below. Each review team will ensure that each part of an application has only one primary reviewer as appropriate.
- For NDAs/sNDAs:
 - The SSMRD review team members will review the primary effectiveness data and safety results from controlled clinical trials
 - DNDP review team members will review the data from consumer behavior studies and the postmarketing safety information, if any, from the United States and outside the United States. The DNDP review team will inform the SSMRD if the DNDP review team identifies a serious safety issue that is not reflected in the prescription labeling.
- Through both IND and NDA stages of drug product development, all review team members will provide their opinions on matters related to their expertise, as well as the suitability and appropriateness of the drug product for nonprescription use.

PROCEDURES

Pre-IND

- All requests by sponsors to discuss nonprescription marketing of any drug product under an approved NDA (whether currently existing as a prescription drug product or not) typically will be addressed with a pre-IND meeting depending on the stage of drug product development. The DNDP chief, project management staff (CPMS) should be the initial contact for the sponsor and the assigned DNDP regulatory project manager (RPM) will be the OND regulatory contact thereafter. Upon submission by the sponsor, a pre-IND file number will be assigned and the RPM will respond to the meeting request.
- Based on the pre-IND meeting discussion, DNDP will advise the sponsor on whether an IND should be submitted to support development or if sufficient information is available to proceed with an NDA. Additional meetings may be beneficial as the development program progresses.
- If the drug product is already approved as a prescription drug product, all submissions related to the switch to nonprescription marketing should be submitted to DNDP under an IND or a pre-IND if an IND is not needed.

Drug Product Development Under the Pre-IND or IND

The Review Team

- Processing and Review
 - The DNDP RPM will review incoming submissions and determine the appropriate SSMRD to perform a collaborative review.
 - The DNDP RPM will contact the SSMRD's CPMS and provide basic information about the submission (e.g., meeting request, new protocol) and the type of review work that is likely to be required from the SSMRD (e.g., medical officer review of a protocol for clinical efficacy). The DNDP RPM will communicate relevant review goal dates associated with the submission such as user fee goal dates. A formal consult request is not needed for a collaborative review.
 - Table 1 provides a general representation of the collaborative review assignments that are the responsibility of the review staff within DNDP and the SSMRD. If an SSMRD reviewer is assigned to participate, the

assignment will be designated in the appropriate electronic archival system.

Table 1. Collaborative Review Assignments

Subject	Review Responsibility
Clinical Efficacy	SSMRD*
Clinical Safety From clinical trials From postmarketing and consumer behavior studies	SSMRD DNDP
Clinical Pharmacology	SSMRD
Consumer Behavior	DNDP
Drug Facts Labeling	DNDP
Pharmacology and Toxicology	DNDP
Statistics From clinical efficacy and safety From consumer behavior studies	SSMRD* DNDP

* In some cases the submission or portions thereof will be reviewed by DNDP (e.g., simulation studies for sunscreens and antiseptics).

- Final recommendations from the SSMRD should reflect the position of the SSMRD management.
- The SSMRD or DNDP review team may recommend that the DNDP RPM consult different divisions for specific questions pertaining to the submission. If a consult is determined to be needed, the DNDP RPM will issue a formal consult request in accordance with established OND procedures.
- All assigned reviewers are part of the review team and will be included in all IND development meetings (internal and external) and team discussions, as appropriate. Ideally, the review team will remain the same from early drug product development under the IND (or pre-IND) to NDA review to maintain historical knowledge of the development program throughout the drug product life cycle.
- SSMRD Assignment
 - The SSMRD CPMS will serve as the point of contact for the DNDP RPM unless he or she designates an RPM as the SSMRD point of contact
 - The SSMRD CPMS or designated RPM will, in consultation with the SSMRD management, make reviewer assignments within 3 business days of receipt and notify the DNDP RPM of these assignments to help ensure that DNDP meets user fee and other review goals

- The SSMRD CPMS or designated RPM will provide a list of names to the DNDP RPM of additional division staff (i.e., team leaders, division management and/or office management) whose participation is deemed necessary
- After reviewer assignments are identified, the DNDP RPM will notify the appropriate SSMRD staff of any new submissions and/or assignments requiring collaborative review with DNDP

Sponsor Meeting Preparation and Conduct

- The DNDP RPM will schedule and facilitate all meetings
- All meetings will be scheduled and conducted according to current OND meeting management practices and goals
- Preliminary responses and meeting minutes:
 - The DNDP RPM will circulate all preliminary responses to sponsor questions and meeting minutes for revision and concurrence by all meeting attendees including the meeting chair (e.g., DNDP division director). Finalization of the preliminary responses and meeting minutes are in accordance with user fee goal dates.
 - Comments from the SSMRD should reflect the position of the SSMRD division and not only the opinion of an individual reviewer.
 - The DNDP RPM will manage all meeting-related documents and help ensure that any conflicts are brought to the attention of the DNDP Director or Deputy Director for resolution.
 - The DNDP Director or designee will provide final clearance on preliminary responses and meeting minutes. When substantive changes are made to the recommendations of the SSMRD, the DNDP Director or designee will ask the SSMRD to review the changes.

Marketing Applications

- DNDP will receive all new drug applications (NDAs/sNDAs) for marketing a nonprescription drug product.
- Upon receipt of such marketing application, the DNDP RPM will determine whether SSMRD review assignments are needed. SSMRD review assignments will follow the procedures described in the Drug Product Development Under the Pre-IND or IND section.

- Managing and Tracking the Review

The DNDP RPM will schedule review team meetings consistent with the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*¹ and the CDER 21st Century Review Process Desk Reference Guide. All members of the review team are expected to adhere to the review schedule agreed to by the review team members and good review management practice expectations. Meetings (including face to face, formal teleconferences, and videoconferences) with the applicant during the review process should include members of the review team.

- New Drug Application for a Nonprescription Drug Product That Is First-in-Class

The SSMRD team members will participate in all review team functions. For the application review key meetings (e.g., filing, mid-cycle, and wrap-up meetings), management should be present from both the division and office levels of DNDP and the appropriate SSMRD and ODE.

- New Drug Application (NDA/sNDA) for a Nonprescription Drug Product That Is Not First-in-Class

The SSMRD team members will participate in all review team functions. The SSMRD division director (or designee) will be invited to application review milestone meetings to discuss any deficiencies and provide a recommendation to the signatory authority on the appropriate regulatory action.

- Advisory Committee Meetings

In general, any application for a first-in-class nonprescription drug product would be considered for review by an FDA advisory committee panel that includes the full Nonprescription Drugs Advisory Committee (NDAC). Depending on the subject matter, the review team may choose to include a full committee from the representative SSMRD or certain members of those committees who can complement the discussion with their particular subject matter expertise. The meeting will be chaired by the NDAC chairperson.

¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

- Supervisory Review and Decision Making
 - First-in-Class Nonprescription Drug Products
 - The DNDP RPM will circulate the action package for supervisory review by the directors of DNDP, the SSMRD, and relevant ODEs.
 - The DNDP Director or Deputy Director and the SSMRD director or deputy director will either write a summary decisional review outlining the recommendation of his or her division or indicate concurrence by signing the review team's summary review (for example, the review of the cross-discipline team leader or the integrated team review).
 - The ODE directors or deputy directors will write summary decisional reviews or they will indicate concurrence with the team's recommendations by signing the review team's summary review. The ODE directors or deputy directors will also jointly sign the regulatory action letters. In certain circumstances, but not in the case of new molecular entity NDAs, the ODE IV Director and the director of the responsible SSMRD ODE may determine that an office-level signature is not necessary. In these cases, the DNDP Director and the SSMRD director will jointly sign the regulatory action letter. The summary decisional reviews by the DNDP Director and/or Deputy Director and the SSMRD director and/or deputy director will capture the decision to down delegate final signatory authority on the application.
 - New Molecular Entity NDAs That Are Not First-in-Class Nonprescription Drug Products
 - The DNDP RPM will circulate the action package for supervisory review by the ODE IV Director or Deputy Director
 - The DNDP Director or Deputy Director and the SSMRD director or deputy director will each write a summary decisional review outlining the recommendation of his or her division or indicate concurrence with the team's recommendation by signing the review team's summary review
 - The ODE IV Director or Deputy Director will sign the regulatory action letters for these applications and will be responsible for either writing the summary decisional review supporting the Office's regulatory decision or indicating concurrence with the team's recommendation by signing the review team's summary review

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- All Other NDAs/sNDAs for Nonprescription Drug Products
 - The DNDP RPM will circulate the action package for supervisory review by the DNDP Director or Deputy Director
 - The DNDP Director or Deputy Director will sign the regulatory action letters for these applications and will be responsible for either writing the summary decisional review supporting the Division’s decision or indicating concurrence with the team’s recommendation by signing the review team’s summary review
 - General Comments Regarding Recommendations From the SSMRD
 - Final recommendations from the SSMRD should reflect the position of the SSMRD management and address approvability of the application (e.g., history of the Rx drug product, data in the application as a whole).
 - If there are disagreements between DNDP and the SSMRD, the disagreements will be resolved as described in MAPP 4151.2 Rev. 1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.*

Postapproval Oversight of Nonprescription Drug Products Marketed Under an Approved NDA

- Nonprescription drug products approved under an NDA will remain the responsibility of DNDP.
- Chemistry supplements for these drug products will be reviewed by the designated Office of Pharmaceutical Quality reviewers assigned to DNDP.
- DNDP will review postmarketing periodic safety reports and evaluate the need for revisions to the nonprescription drug product labeling.
- If an applicant requests additional nonprescription claims or variations on the original claim, the review of such requests will be conducted in collaboration with the SSMRD, as appropriate, and will proceed as outlined previously in the Procedures section. Whenever possible, the same SSMRD reviewers and DNDP reviewers who served on the initial review team should be assigned to review postapproval changes.

Resolution of Differing Professional Opinions

- See MAPP 4151.2 Rev. 1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director* for a discussion on dispute resolution.

REFERENCES

1. MAPP 6020.8 Rev. 1 *NDA/BLAs/Efficacy Supplements: Action Packages and Taking Regulatory Actions*
2. MAPP 4180.4 *NDA/BLAs: Using the 21st Century Review Process Desk Reference Guide*
3. MAPP 4151.1 Rev.1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*
4. MAPP 4151.2 Rev. 1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director*

DEFINITIONS

- **Collaborative Review.** One or more divisions other than the lead division contribute resources to an IND or NDA review team to review a specific portion of the submission (e.g., chemistry, manufacturing, and controls; clinical pharmacology; clinical).
- **Consultative Review.** One or more divisions contribute resources to answer limited and specific questions (such as the validity of a particular clinical endpoint or to determine the abuse potential of a drug) outlined in a consultative request issued by an IND or NDA review team.
- **First-in-Class Nonprescription Drug Product.** A proposed drug product that, if approved, would be the first in its pharmacological class to be marketed without a prescription or that would be intended for an indication not applicable to any legally marketed nonprescription drug product.
- **Initial Marketing of a Nonprescription Drug Product.** This drug product category can be one of two types: (1) nonprescription marketing of a drug product that was never previously marketed as a prescription drug product; or (2) nonprescription marketing of a drug product in a strength, dose, schedule, route of administration, duration of use, population, indication, or dosage form different

from ones previously approved for prescription use. See also the definition of *Rx-to-OTC Switch*.

- **New Molecular Entity.** A new molecular entity is an active ingredient that contains no active moiety that has been previously approved by the FDA in an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act or has been previously marketed as a drug in the United States.
- **Nonprescription Drug Actual Use Study.** A clinical trial in which a drug product is used by subjects under nonprescription-like conditions.
- **Nonprescription Label Comprehension Study.** A study to evaluate proposed nonprescription drug product labeling. In such studies, no drug product is dispensed to subjects. Such a study is not a clinical investigation as defined under 21 CFR 312.3(b).
- **Nonprescription or OTC Drug Product.** A drug product marketed for use by consumers without the intervention of a health care professional (a prescription) to obtain the drug product.
- **Prescription or Rx Drug Product.** A drug product approved for marketing that can be obtained only with a prescription from an appropriately licensed health care professional.
- **Rx-to-OTC Switch.** The nonprescription marketing of a drug product that was previously a prescription drug product for the same indication, strength, dose, schedule, duration of use, dosage form, population, and route of administration; or the nonprescription marketing of a drug product whose active ingredient has a history of prescription marketing but for a different indication, strength, dose, schedule, duration of use, dosage form, population, and/or route of administration than the proposed nonprescription drug product.
- **Specific Subject Matter Review Division (SSMRD).** The OND review division with primary oversight of a group of prescription drug products directed at physiologically categorized diseases (e.g., cardiovascular drug products).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
1/15/97	N/A	
7/12/07	Rev. 1	Revised to reflect OND reorganization and assignment of nonprescription drug product applications to the Office of Nonprescription Products.
06/25/18	Rev. 2	In addition to editorial changes, names of offices and divisions were updated.