**OFFICE OF NEW DRUGS**

# Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products

## CONTENTS



## 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 new drug applications (NDAs) 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

- In January 1997, MAPP 6020.5 established a process for the review of NDAs for over-the-counter (OTC) products that combined the consumer comprehension and behavioral expertise of the Division of Over-the-Counter Drug Products (DOTCDP) with the clinical and scientific expertise of the specific subject matter review division (SSMRD). This process required the SSMRD and the DOTCDP to review and co-sign action letters for these types of NDAs. The SSMRD was assigned as the lead division in the coordination of the review of any IND or NDA submission before approval. The DOTCDP was assigned as the lead division in the coordination of the review of any NDA submission post-approval.

- In May 2005, OND reorganized. As a part of this reorganization, the DOTCDP became the new Office of Nonprescription Products (ONP). Although OND as a whole continues to hold responsibility for the timely review and regulation of nonprescription products, the OND Director assigned ONP as the lead office for these applications.

## DEFINITIONS

- **Advisors and Consultants Staff.** The staff responsible for managing the external advisors and consultants to the Center for Drug Evaluation and Research (CDER). This staff reports directly to the Director, Office of Executive Programs, and is a part of the immediate office of the Center Director.

- **Applicant.** See 21 CFR 314.3.

- **Chief, Project Management Staff (CPMS).** This individual is the first-line supervisor for the project management staff in each review division.

- **Clinical Investigation.** See 21 CFR 312.3(b).

- **Collaborative Review.** One or more divisions other than the lead division contribute resources to an IND or NDA review team to review a critical portion of the submission (e.g., chemistry, manufacturing, and controls (CMC); pharmacology and toxicology; 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 appropriateness of a proposed trade name) outlined in a consultative request issued by an IND or NDA review team.

- **Division of Nonprescription Clinical Evaluation (DNCE).** The ONP division whose primary responsibility is the review management and oversight of INDs and NDAs for nonprescription drug products.

- **Division of Nonprescription Regulation Development (DNRD).** The ONP division whose primary responsibility is the development of monographs through regulation as part of the OTC drug review.

- **First-in-Class Nonprescription Product.** A proposed 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 previously approved nonprescription drug product.

- **Initial Marketing of a Nonprescription Drug Product.** This product category can be one of two types: (1) nonprescription marketing of a product that was never previously marketed as a prescription drug product, or (2) nonprescription marketing of a 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 definition of *Rx-to-OTC Switch*.

- **Nonprescription Drug Actual Use Study.** A clinical trial in which a drug 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.

- **Office of Biostatistics (OB).** The CDER office responsible for the statistical evaluation of data submitted to INDs and NDAs.

- **Office of Clinical Pharmacology (OCP).** The CDER office responsible for the evaluation of pharmacokinetic and biopharmaceutic data submitted to INDs, NDAs, and biologics license applications (BLAs).

- **Office of New Drug Quality Assessment (ONDQA).** The CDER office responsible for the evaluation of CMC data submitted to INDs and NDAs.

- **Office of New Drugs (OND).** The CDER office that serves as the primary regulatory authority for the clinical and nonclinical evaluation of INDs, NDAs, and BLAs.

- **Office of Nonprescription Products (ONP).** As of May 2005, the OND office that is responsible for the drug development oversight of nonprescription drug products, the review of NDAs intended for nonprescription drug products, and the promulgation of regulations concerning OTC drug monographs (see 21 CFR 330).

- **OTC or Nonprescription Drug Product.** A drug product marketed for use by consumers without the intervention of a health care professional (a prescription) to obtain the product (hence, an *over-the-counter* or *nonprescription* product).

- **Rx Drug Product.** A drug product approved for marketing that can be obtained only with a prescription (Rx) from an appropriately licensed health care professional.

- **Rx-to-OTC Switch.** The nonprescription marketing of a 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 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 product.

- **Specific Subject Matter Review Divisions (SSMRDs).** Those OND review divisions with primary oversight over a group of Rx drug products directed at physiologically categorized disease entities (e.g., cardio-renal drug products, neuropharmacologic drug products).

- **Sponsor.** See 21 CFR 312.3.

## POLICY

- ONP will oversee the review and regulatory action on INDs and pending or approved NDAs for all nonprescription products, including Rx-to-OTC switches.

- ONP will obtain collaborative review resources for scientific advice as needed from OND and other CDER offices. All reviewers as assigned by ONP and the SSMRD will be officially designated in appropriate tracking systems.

- ONP will oversee the drug development programs carried out under INDs for nonprescription drugs. As part of this oversight, the DNCE will manage all meetings related to nonprescription drug products (approved or potential).

- ONP will determine and inform sponsors when the submission of a new IND will be necessary for the development of a nonprescription product.

  – In general, if a clinical study (including an actual use study) is determined to be a necessary part of the development plan, a new IND will need to be established in ONP.

  – If a label comprehension study is the only study that needs to be conducted, an IND does not need to be established and this study can be submitted in the new NDA. However, if a sponsor wishes to submit a protocol for a label comprehension study for FDA review and comment before initiating the study, the protocol can be submitted to a new pre-investigational new drug application (pre-IND) established in ONP.

- The ONP or the ONP review divisions will sign the regulatory action letters for all NDAs for nonprescription products except those applications that represent a first-in-class nonprescription product. Decisions on first-in-class nonprescription product NDAs will be a dual sign-off between ONP and the Office of Drug Evaluation (ODE) with regulatory oversight of the prescription product, unless otherwise stated (see below).

## RESPONSIBILITIES

- The DNCE is responsible for the administration of INDs and marketing applications (either original NDAs or efficacy supplements) for nonprescription drug products. The DNCE's administrative responsibilities include meeting management and facilitating active participation on the IND and NDA review teams by appropriate staff from both the DNCE and the SSMRD.

- The DNCE will form an IND or NDA review team responsible for the review of INDs and marketing applications. This team will include appropriate members from the SSMRD. The review team is responsible for deciding which members will review the various sections of an application, consistent with the general review procedures described below. The review team will ensure that each part of the application has only one primary reviewer.

- Ordinarily, the SSMRD review team members are responsible for the review of primary effectiveness data and safety results from controlled clinical trials.

- The DNCE review team members are responsible for the review of data from consumer behavior studies and the review of postmarketing safety experience, if any, both in the United States and worldwide.

- All review team members are responsible for providing their opinions on the suitability and appropriateness of the product for nonprescription use.

## PROCEDURES

- Since the DNCE is responsible for the administration of INDs and marketing applications (either original NDAs or efficacy supplements) for nonprescription drug products, the DNCE administrative policies and procedures will be used (i.e., time frame for scheduling and holding meetings, process for communicating with sponsors and applicants). The DNCE and the SSMRD will ensure effective collaboration.

### A. Pre-IND

- All requests by sponsors to discuss nonprescription marketing of any drug product under the authority of an approved NDA (whether currently existing as an Rx product or not) will be addressed with a pre-IND meeting. The DNCE CPMS is the initial contact for the sponsor and the assigned DNCE regulatory project manager (RPM) will be the OND regulatory contact thereafter. The DNCE RPM will assign a pre-IND number and schedule the meeting.

- The pre-IND meeting will determine whether the sponsor needs to open an IND with the DNCE to complete development or whether it can prepare an NDA for submission. If an IND is required, additional meetings may be beneficial as the development program progresses.

- If the product is already approved as a prescription product, all submissions related to the switch to nonprescription marketing should be submitted to the IND with the DNCE or to the pre-IND number if an IND is not needed.

### B. IND and Pre-NDA

1. The Review Team

- Processing and Review

  – The DNCE RPM will review incoming submissions and determine which SSMRD is needed to perform a collaborative review.

  – The DNCE RPM will contact the SSMRD CPMS and provide information about the relevant submission (e.g., pre-IND meeting request, IND protocol submission, new NDA) 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 DNCE RPM will also provide any relevant dates (e.g., receipt date of the submission, 14-day date to schedule meeting by, filing date, date of 30-day clinical hold notification), particularly Prescription Drug User Fee Act (PDUFA) goal dates.

- Table 1 provides a general representation of the collaborative review assignments that are the responsibility of the review staff within DNCE and the SSMRD. If an SSMRD is requested to participate, the request will be designated in the appropriate database.

**Table 1. Collaborative Review Assignments**

| Subject | Review Responsibility |
|---|---|
| Clinical Efficacy | SSMRD[1] |
| Clinical Safety | |
| From clinical trials | SSMRD |
| From postmarketing and consumer behavior studies | DNCE |
| Consumer Behavior | DNCE |
| Drug Facts Labeling | DNCE |
| Pharmacology and Toxicology | DNCE[2] |
| Microbiology | |
| In vitro antimicrobial studies | DNCE |
| In vitro antifungal and antiviral studies | SSMRD |

[1] In some cases (e.g., simulation studies for sunscreens and antiseptics), the submission or portions of the submission will be reviewed by the DNCE.
[2] The DNCE will review pharmacology and toxicology data if appropriately staffed and unless there are circumstances that warrant maintaining the review in the SSMRD.

- Final recommendations from the SSMRD should reflect the position of the SSMRD management.

- The SSMRD will notify the DNCE RPM of any consults necessary for the review of assigned material.

- All assigned reviewers are part of the review team and will be included in all IND development meetings (internal and external) and team discussions. Ideally, the review team will remain the same during IND development and NDA review to maintain historical knowledge of the development programs throughout the product life cycle.

- SSMRD Assignment

  - The SSMRD CPMS will serve as the point of contact for the DNCE RPM unless he or she designates an SSMRD RPM to follow the project and be the point of contact for the SSMRD.

  - The SSMRD CPMS or designated RPM will, in consultation with the SSMRD management, make timely reviewer assignments and notify the DNCE RPM of

these assignments to help ensure that ONP meets PDUFA and other associated goals.

- The SSMRD CPMS or designated RPM will provide a list of names to the DNCE RPM of additional division staff (i.e., team leaders, division management and/or office management) whose participation is deemed necessary.

- The SSMRD CPMS or designated RPM will notify the appropriate SSMRD staff of any new submissions and/or assignments involving a collaborative integration with the DNCE.

2. Meeting Preparation and Conduct

- The DNCE RPM will schedule and facilitate all meetings.

- All meetings will be scheduled and conducted according to current OND meeting management practices.

- Meeting Minutes

  - The DNCE RPM will circulate all meeting minutes within 14 days of the meeting for revision and concurrence by **all** meeting attendees and the appropriate division director and deputy director.

  - The DNCE RPM will send the meeting minutes via e-mail to the SSMRD CPMS or designated RPM and will include a list of the SSMRD meeting attendees and a goal date for comments to be returned. Finalization of meeting minutes must meet PDUFA goals.

  - The SSMRD CPMS or designated RPM will circulate the meeting minutes through the SSMRD meeting attendees and to the division and/or deputy director for review, editing, and concurrence. Comments from the SSMRD should reflect the position of the division and not just the opinion of the individual reviewer.

  - The SSMRD contact will send one version of the meeting minutes containing all SSMRD revisions to the DNCE RPM. Receipt of the revised meeting minutes from the SSMRD contact will convey concurrence by the SSMRD management. The DNCE RPM will review and incorporate the edits and comments and bring any conflicts to the DNCE Director for resolution.

  - The DNCE Director or designee will approve meeting minutes.

## C. NDA

- The DNCE will receive all submitted applications for marketing a nonprescription product.

- Upon receipt of an NDA, the DNCE RPM will obtain review assignments within ONP and determine what SSMRD review assignments are needed. SSMRD review assignments will follow the procedures in Section B.

- Managing and Tracking the Review

  The DNCE 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] All members of the review team are expected to adhere to the schedule agreed to by the review team members and good review management practice (GRMP) expectations. Meetings (including face to face, formal teleconferences, and videoconferences) with the applicant during the review process should include all pertinent members of the NDA review team.

  – First-in-Class Nonprescription Product NDAs

    The SSMRD team members will fully participate in all review team functions. For the filing, mid-cycle, and wrap-up meetings, management should be present from both the division and office levels of ONP and the appropriate SSMRD and ODE.

  – NDAs for a Nonprescription Product that Is Not First in Class

    SSMRD team members will participate in all review team functions. The SSMRD division director (or designee) will be invited to the filing, mid-cycle meeting, and wrap-up meeting to discuss the deficiencies and provide a recommendation on the appropriate regulatory action.

- Advisory Committee Meetings

  In general, any application for a first-in-class nonprescription product may 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 directors of the DNCE, ONP, SSMRD, and relevant ODE along with the review team may also choose to include a full committee from the representative SSMRD or may elect to include certain members of those advisory committees who can complement the discussion with their particular subject matter expertise. The meeting will be chaired by the NDAC chairperson.

- Supervisory Review and Decision Making

  – First-in-Class Nonprescription Product NDAs

    · The DNCE RPM will circulate the action package for supervisory review by the directors of the DNCE, ONP, SSMRD, and relevant ODE.

[1] 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.

- The Director and/or Deputy Director of the DNCE and of the SSMRD will each write a summary decisional review outlining the recommendation of his or her division.

- Summary decisional reviews will be written by the ONP Director or Deputy Director and the appropriate ODE director or deputy director.

- The regulatory action letters for these applications will be signed jointly. The ONP Director or Deputy Director and the ODE director or deputy director that oversees the work of the collaborating SSMRD will sign the action letters for these NDAs.

  - In certain circumstances, but not in the case of new chemical entity NDAs, the Director of ONP and of the ODE that oversees the work of the collaborating SSMRD may determine that an office-level signature is not necessary. In these cases, the Director of the DNCE and of the SSMRD will sign the action letter. The summary decisional reviews written by the Director and/or Deputy Director of the DNCE and of the SSMRD should capture the decision to reassign final office clearance. The regulatory action letters for these applications will still be signed jointly.

– New Chemical Entity NDAs that Are Not First-in-Class Nonprescription Products

  - The DNCE RPM will circulate the action package for supervisory review by the ONP Director.

  - Only the ONP Director or Deputy Director will sign the action letters for these applications. The ONP director who signs the application is responsible for writing the summary decisional review supporting the office's decision.

    - The Director and/or Deputy Director of the DNCE and of the SSMRD will each write a summary decisional review outlining the recommendation of his or her division.

– All other NDAs

  - The DNCE RPM will circulate the action package for supervisory review by the DNCE Director or Deputy Director, or in some cases to the DNRD Director or Deputy Director.

  - Only the DNCE Director or Deputy Director, or in some cases the DNRD Director or Deputy Director, will sign the regulatory action letters for these applications. The director who signs the application is responsible for writing the summary decisional review supporting the division's decision.

- General Comments on Recommendations from the SSMRD

  - Final recommendations from the SSMRD should reflect the position of the SSMRD management. Recommendations should address approvability and should be based on material reviewed by the SSMRD and the SSMRD opinion (e.g., history of the Rx product, data in the application as a whole). It is expected that during the course of the review, the SSMRD division director or designee will be aware of the totality of the data, not just those data reviewed by the SSMRD, and the recommendations of the individual reviewers and team leaders through regular meetings as outlined by the GRMPs.

  - If the recommendations are reflected in the SSMRD reviews, the SSMRD division director should sign off on the review and make a statement of concurrence or, alternatively, write a brief memo of concurrence.

  - If the SSMRD division director does not agree with the recommendation in the SSMRD review, the division director or designee should write a review outlining the disagreements. The review should include the recommendation of the division and the rationale for the recommendation.

  - If there are disagreements between the DNCE and the SSMRD, the disagreements will be resolved as described in Section E.

**D. Post-Approval Oversight of Nonprescription Drug Products Marketed under the Authority of an Approved NDA**

- Nonprescription drugs approved under an NDA will remain the responsibility of the DNCE.

- Chemistry supplements for these products will be reviewed by the ONDQA reviewing chemists assigned to ONP.

- The DNCE will review postmarketing periodic safety reports and revise the product's nonprescription labeling.

- If an applicant requests additional nonprescription claims or variations on the original claim that require the review of clinical or pharmacology and toxicology data, 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 DNCE reviewers who served on the initial NDA review team should be assigned to review post-approval changes.

**E. Resolution of Disagreements**

- If there are disagreements between the DNCE and the collaborating SSMRD based on interpretation of the supporting scientific data and the appropriate regulatory action, the DNCE Director should attempt to resolve these differences with the SSMRD director as soon as possible.

- Reviews by the NDA review team members should be completed according to the agreed upon timelines regardless of any disagreement between the DNCE and the SSMRD. The NDA review team should consider a Regulatory Briefing if disagreements exist and there is the possibility that the application will go to the OND Director for final signature on the action.

- Table 2 outlines the management pathway to resolve disagreement on the final regulatory action or labeling.

**Table 2. Management Pathway to Resolve Disagreements**

| Subject of Disagreement | First in Class | Not First in Class |
|---|---|---|
| Final Regulatory Action | Step 1: Office Directors[1]<br>↓<br>Step 2: OND Director or Deputy Director[2] | Step 1: Office Directors[1]<br>↓<br>Step 2: OND Director or Deputy Director[2] |
| Labeling | ONP Director | DNCE Director |

[1] If agreement cannot be reached between divisions, the ONP Director will initiate a discussion with the appropriate ODE director to attempt to resolve differences. If the ONP Director reaches agreement with the relevant ODE director, and the resulting action differs from the opinion of the DNCE, then the ONP Director will sign the action letter.
[2] Signs letter if he or she makes final decision.

- A summary of these differences of opinion and justification for the final decision will be included in the summary review that is written by the official who signs the action letter.

## EFFECTIVE DATE

This MAPP is effective upon date of publication.