

OFFICE OF NEW DRUGS

Action Packages for NDAs and Efficacy Supplements

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PURPOSE

This MAPP outlines policies and procedures designed to:

- Facilitate final review of new drug applications (NDAs) and efficacy supplements
 - Establish what constitutes a complete action
 - Establish consistent format and content of action packages for NDAs and efficacy supplements
 - Establish procedures for circulation of and concurrence on action packages for NDAs and efficacy supplements
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BACKGROUND

- The action package for NDAs and efficacy supplements was developed to facilitate final review and decisions on NDAs and efficacy supplements.
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DEFINITIONS

- **Action package:** A compilation of (1) FDA-generated documents related to review of an NDA or efficacy supplement (i.e., from submission to final action), (2) documents (e.g., meeting minutes, pharmacology reviews) pertaining to the format and content of the application generated during drug development (investigational new drug (IND)), and (3) labeling submitted by the applicant.
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- **Action package checklist:** A table of contents and administrative summary for the action package. The checklist is located in the CDER Standard Letters System.
 - **Final review:** A review that has been checked into the Document File System (DFS) and has received all appropriate signatures.
 - **Action goal date:** The date the review team has selected to issue an action letter for a pending application. When a date has not been selected, the action goal date defaults to the user fee goal date.
 - **User fee goal date:** The date by which an action is due on a marketing application under the time frames negotiated as a result of the Prescription Drug User Fee Act of 1992 and subsequent legislation amending that act.
 - **Act on:** The issuance of an action letter after the filing of an application.
 - **Action letter:** An approval letter (21 CFR 314.105), an approvable letter (21 CFR 314.110), or a not approvable letter (21 CFR 314.120) issued after complete review of the application.
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POLICY

- An action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in suitable condition for approval.
- With the exception of minor editorial changes, there must be agreement on the labeling text between the Agency and applicant at the time of application approval. Minor editorial changes are those that could appropriately be included in an annual report.
- If the agreed upon labeling text or final printed labeling is available in electronic format, it will be attached to the approval letter.
- An action package will be compiled in the order defined by the Action Package Checklist (located in the CDER Standard Letters System) for all NDAs and efficacy supplements. For each review cycle, all documents generated during that cycle should be added to the action package prior to review by the signatory authority. Drug Master File (DMF) reviews and letters and faxes to DMF holders are not included in the action package. However, these documents should be available to the chemistry reviewer on request. In the case of a collaborative review that involves more than one new drug review division or two centers, a single action package will be compiled for an application.

- An action package will include only those items described in this MAPP that are pertinent to the application.
- An action package is not a complete administrative record of the review of an application, because it generally does not include all documents related to the review. For example, although establishment evaluation summaries are included, establishment inspection reports are not.
- IND reviews referenced in NDA reviews will be included in the action package.
- The review time line will provide sufficient time for action package compilation, circulation for concurrence, and final review. Applications for office level sign-off should be delivered for office review at least 3 weeks in advance of the action goal date for standard review applications and 2 weeks in advance for priority review applications, unless an alternative time frame is agreed to by the division and office. Time lines and action package circulation may need to be adjusted for dual office or division sign-off.
- All reviews will be considered final at the time an action is taken on an application. In the rare instance where a review is interrupted before the reviewer has made it final (e.g., because of illness), the review will nonetheless be checked into DFS prior to or at the time of the action with a written explanation by the reviewer or team leader on the state of the review.
- Before taking an action on an application, all requested facility inspections must have progressed sufficiently that a recommendation from the Division of Manufacturing and Product Quality can be documented (in the Establishment Evaluation System or by other means). An attempt to schedule an inspection that is declined by the facility representative (e.g., because of lack of readiness) is considered a completed inspection and will be documented in the inspection summary.
- The Division of Scientific Investigation (DSI) will provide the review division with a summary review of any clinical or nonclinical inspection information prior to an action on an application. Before an action, the inspection process must have progressed sufficiently that the DSI scientific reviewer can provide an inspection summary review that relates to the usability of data. An attempt to schedule an inspection that is declined by the site representative (e.g., because of lack of readiness for the inspection) is considered an unacceptable situation resulting in unusable data.
- An application may be acted on before facility, clinical, or nonclinical inspections have progressed to the point where usability of data is determined if any of the deficiencies found during the course of review of any of the technical sections of the application, taken alone or in the aggregate, are of such magnitude that, in the

judgment of the Agency, it will require 1 year or longer for the applicant to submit a complete response. Examples include, but are not limited to the need to repeat or conduct a clinical trial or preclinical carcinogenicity study.

- A scientific review of an application is considered a reviewer's own work and cannot be altered by division management or the reviewer once it is final. Disagreements by team leaders, division directors, or office directors with any or all of a reviewer's major conclusions must be documented in a separate review or in an addendum to the review.
- All action packages will include a summary review that documents conclusions from all reviewing disciplines about the drug product, noting any critical issues and disagreements with the applicant and how they were resolved, recommendation for action, and an explanation of any nonconcurrency with review conclusions. The summary review will generally be done by the medical team leader for applications where the division director is the signatory authority and by the medical team leader or the division director where the office director is the signatory authority. Where the division director or office director has not written a separate review, he or she should write a brief statement of concurrence with the summary review or signify concurrence with signature comments if the review is routed through DFS for signature. If the signatory authority disagrees with the conclusions or the recommendations made by the summary reviewer or wants to add further analysis of particular points, a separate review must be written to document this.
- Applications should be complete when submitted, but the need for additional information is often identified during a review, leading to one or more amendments. Reviews of the original submission must be complete by the time of the first action, but it is the review division's decision whether to review an amendment in the review cycle in which it is received or to defer review to the next review cycle.

RESPONSIBILITIES

New Drug Review Division Staff

The **Regulatory Project Manager** (RPM) is responsible for:

- Compiling the action package. In the case of a collaborative review, the project manager for the lead division will compile the action package.
- Filling out the action package checklist
- Ensuring that all applicable documents are included in the action package

- Requesting submission of an electronic version of the agreed upon labeling text in MS Word and PDF format to the electronic document room (EDR)
- Completing the Waxman-Hatch exclusivity summary and obtaining the division director's signature on the summary for approval actions
- Coordinating circulation of the action package within the division
- After an approval action, notifying the Document Room Liaison that an action package is ready for photocopying (refer to MAPP 4520.1, Communicating Drug Approval Information)

The **Chief, Project Management Staff** (CPMS), is responsible for:

- Ensuring that action packages are completed for all NDAs and efficacy supplements (SE1-SE8)
- Ensuring that action packages where the division director is the signatory authority meet CDER policies and drug regulations

The **Review Team** is responsible for:

- Providing sufficient time in the application review time line for compilation, circulation, and review of the action package

The **Reviewer** is responsible for:

- Ensuring that reviews are in final form before action is taken on an application (checked into and signed in DFS). In the rare situation where a review is interrupted (e.g., because of illness), the reviewer will check the review into DFS for appropriate signatures with a written explanation on the status of the review. If the reviewer is unable to do this, that responsibility will shift to the team leader.
- Providing as attachments to their reviews any IND reviews, minutes of meetings held during drug development, or other IND documents that are referenced in the review

The **Team Leaders** are responsible for:

- Ensuring that all reviews for their disciplines are final and checked into DFS with all appropriate signatures completed before an action. In the rare situation where a review is interrupted (e.g., because of illness), and the reviewer cannot check the review into DFS, the team leader is responsible for checking the review into

DFS with a written statement on the status of the review, and for ensuring that appropriate signatures are completed prior to the action.

- Ensuring that reviews for their disciplines address applicable regulations and policies and are scientifically sound
- For actions where the division director is the signatory authority or when assigned for actions where the office director is the signatory authority, the **medical team leader** is responsible for writing a summary review on the drug product, documenting conclusions from all reviewing disciplines and noting any critical issues and disagreements with the applicant and how they were resolved. If issues or disagreements are still pending, the team leader will describe existing conditions. An explanation for any nonconcurrency with reviewer conclusions and a recommendation for action will be included.

The **Division Director** is responsible for

- Writing a summary review or assigning the medical team leader the responsibility for writing a summary review for each action where the division director or office director is the signatory authority. The summary review will document conclusions about the drug products from all reviewing disciplines, noting any critical issues and disagreements with the applicant and how they were resolved, and explaining any nonconcurrency with reviewer conclusions. For applications where the office director is signatory authority, the status of any pending issues or disagreements will be included.
- Writing a brief statement of concurrence with the summary review (may be done by adding signature comments if the review is routed to the division director through DFS) or writing a separate review documenting the basis for the action if the division director as signatory authority disagrees with the conclusions or recommendations made by the medical team leader.

Document Room Staff (DDR)

Document Room Staff is responsible for:

- Ensuring that three copies of the action package are made and distributed according to the procedures in MAPP 4520.1, Communicating Drug Approval Information, upon notification by the project manager that the application has been approved

Office Staff

The **Director, Office of Biostatistics**, and the **Director of Biopharmaceutics** are responsible for:

- Ensuring that reviews of statistical information and clinical pharmacology information address applicable regulations and policies. This review is generally concluded prior to submitting the action package to the signatory authority for review.

The **Associate Directors for Regulatory Affairs** (ADRA) in the Offices of Drug Evaluation and Research, Offices of Drug Evaluation (ODEs I-V), are responsible for:

- Ensuring that action packages where the signatory authority is the office director meet CDER policies and drug regulations
- Coordinating circulation of action packages at the office level for review

The **Associate Director for Pharmacology/Toxicology** is responsible for:

- Ensuring that reviews of nonclinical pharmacology/toxicology information address applicable regulations and policies consistently across the ODE for applications where the office director is the signatory authority

The **Division Director in the Office of New Drug Chemistry** associated with the ODE is responsible for:

- Ensuring that reviews of chemistry, manufacturing, and controls information address applicable regulations and policies consistently across the ODE for applications where the ODE director is the signatory authority

The **ODE Directors** are responsible for:

- Ensuring that summary reviews are completed for each action where they are the signatory authorities
- Conducting a final review of applications where they are the signatory authorities
- Writing a separate review documenting the basis for the action if they as signatory authorities disagree with the conclusions or recommendations made by the summary reviewer (medical team leader or division director)

PROCEDURES

- **Action Letter:** For all approval letters, the agreed upon labeling text or final printed labeling, if available in electronic format, should be attached to the end of the letter.

- **Action Package**
 - **Content:** The final action package should include all documents generated by FDA related to the application review and labeling specified in the Action Package Checklist.

 - **Format:** The action package is formatted according to the sections and elements detailed in the Action Package Checklist. Tabs should be used to differentiate sections or categories of documents. A colored sheet of paper should be inserted between each review. Documents should be ordered by descending date.

 - **Checklist:** The Action Package Checklist will clearly indicate the status of **each** item (i.e., completed or not applicable). Comments can be added to convey additional information. The Action Package Checklist in the CDER Standard Letters System includes instructions and guidance on item definitions.

- **Circulation of the Action Package and Action Letter:**
 - Division-level action: Circulation is determined by the division. Generally the action package and letter are circulated at minimum to the team leaders for each discipline involved in review of the application.

 - Office-level action: Appropriate portions of the action package will be reviewed by the office director, associate director for regulatory affairs, new drug chemistry director, and associate director for pharmacology/toxicology.

 - Early circulation of all or parts of the action package with draft reviews is acceptable.

 - In the case of a collaborative review (e.g., two divisions or centers), sufficient time for circulation of the action package to the appropriate reviewers should be scheduled in the review time line.

- **Action Package Completion Postapproval:**
 - The signed approval letter and labeling (final printed labeling or approved labeling text) is added to the action package.

 - Within 7 calendar days of approval, the Document Room Liaison is notified by e-mail that the Action Package is ready for photocopying. The e-mail should include the RPM's

name or other contact person, the division name, application number, drug name, location of the package, and the number of volumes in the package.

- Within 7 calendar days of notification, three photocopies of the action package will be made for distribution (one to the Division of Data Management Systems and two to the Division of Information Disclosure Policy (refer to MAPP 4520.1, Communicating Drug Approval Information)).
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EFFECTIVE DATE

This MAPP is effective upon date of publication.