

POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

**NDAs/BLAs/Efficacy Supplements:
Action Packages and Taking Regulatory Actions**

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PURPOSE

- This MAPP outlines policies and procedures intended to:
 - Facilitate the **final review** of documentation needed to support regulatory action for new drug **applications** (NDAs), biologics license applications (BLA)s, and certain **efficacy supplements**¹
 - Establish consistent format and content of **action packages** for NDAs, BLAs, and certain efficacy supplements
 - Establish procedures for the compilation and circulation of action packages to the review team and signatory authority
 - Establish policies and procedures for taking a regulatory action (approval, tentative approval, or complete response)

¹ The first use of all terms that appear in the DEFINITIONS section are bolded.

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- This MAPP describes the responsibilities associated with and the procedures for compiling, circulating, reviewing, and finalizing a paper action package. Similar considerations can be applied to preparing, circulating, and finalizing an electronic action package (in lieu of a paper action package); however, formal processes for electronic action packages have not yet been established.
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BACKGROUND

- The action package for NDAs, BLAs, and efficacy supplements was developed to facilitate final review of FDA communications, reviews, and other documents that provide the rationale behind decisions on pending applications. In addition, after approval, the action package is used to provide certain approval-related communications and review documents to the Division of Information Disclosure Policy (DIDP) staff for public disclosure. The package also provides a convenient reference source for the regulatory history of the action.
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POLICY

Action Packages

- Action packages are required for all original NDAs, BLAs, and efficacy supplements, except for labeling supplements with clinical data and manufacturing supplements with clinical data.
- Action packages will include all reviews and other documents identified in the **action package checklist** (the checklist) that are pertinent to the application. For applications that undergo multiple review cycles, the action package will include all reviews and other documents generated during each review cycle culminating in approval (see the DEFINITIONS section for further information about the contents of an action package and the checklist).
- Action packages will be compiled and circulated through the appropriate review team members and signatory authority according to the timelines established in the Center for Drug Evaluation and Research (CDER) 21st Century Review Process Desk Reference Guide (DRG).

Reviews

- All reviews and communications, including the office or deputy office director review (when applicable), related to the review of NDAs, BLAs, and efficacy supplements will be completed and filed in the official archive according to the timelines established in the DRG.

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- All reviews must be final at the time a regulatory action is taken per the DRG (for rare exceptions, see the Inspections subsection). For complete response actions, the review team determines whether to review an amendment in the review cycle in which it was received or to defer review to the next review cycle.

Inspections

- Before a regulatory action is taken, the inspection process for the clinical sites must have progressed sufficiently to allow the Office of Scientific Investigations (OSI) in the Office of Compliance to provide an inspection review summary on the acceptability of the data.
- As applicable, the inspection process for bioequivalence study sites and nonclinical sites must have progressed sufficiently such that the Office of Scientific Integrity and Surveillance (OSIS) in the Office of Translational Sciences can provide an inspection review summary on the acceptability of the data.
- The Office of Pharmaceutical Quality (OPQ) will make an overall recommendation for product manufacturing facility inspections. This recommendation must be current at the time a regulatory action is taken (see the PROCEDURES section for additional details regarding manufacturing facility assessments).
- In general, all necessary facility, clinical, or nonclinical inspections must be completed before a regulatory action is taken. If necessary inspections cannot be completed before the Prescription Drug User Fee Act (PDUFA)/Biosimilar User Fee Act (BsUFA) goal date because of resource or workload limitations, the regulatory action will be delayed until a recommendation is made. This may result in missing the PDUFA/BsUFA goal date.
- A complete response action may be taken before facility, clinical, or nonclinical inspections have been completed in the following circumstances:
 - A firm was not ready for inspection at the time the FDA tried to schedule the inspection.
 - The FDA is not able to complete the inspection before the PDUFA/BsUFA goal date because of official travel restrictions in effect during the review of the application.
 - Deficiencies found during the 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 FDA, the applicant will require 1 year or longer to submit a complete response to the **action letter**. Examples of such major deficiencies

include, but are not limited to, the need to repeat or conduct a clinical trial or a nonclinical carcinogenicity study. Before a complete response action is taken, the review division will consult with the Office of New Drugs Immediate Office (OND IO) as to the appropriateness of this approach for the specific application. The rationale for taking an action before a recommendation from OPQ/OSI/OSIS will be documented in the **summary review** (see the DEFINITIONS section for what constitutes the summary review).

- In rare circumstances, an approval action may be taken where inspections have not been completed and OPQ/OSI/OSIS cannot make a recommendation because of a lack of data. This action requires an assessment of the public health risks and benefits:
 - The review division will consult with OPQ/OSI/OSIS and the OND IO as to the appropriateness of such an action under the specific circumstances before the approval action is taken.
 - The rationale for approving an application despite a withhold recommendation or in the absence of a definitive inspection recommendation will be documented in the summary review.

Regulatory Action Letters

- A complete response letter will provide, in detail, the specific deficiencies and, where appropriate, the actions necessary to make the application potentially suitable for approval.
- A tentative approval letter will address all conditions of approval and include as an enclosure the agreed-upon labeling text and risk evaluation and mitigation strategy (REMS), when appropriate (see the tentative approval letter template in the CDER Standard Templates (CST) electronic repository for further instructions).
- An approval letter will include as enclosures the agreed-upon labeling text and the REMS, when appropriate.
 - The FDA must be in agreement with the applicant on the final labeling text at the time of approval with the exception of *minor editorial changes*. Minor editorial changes are those that could be appropriately included in an annual report, as indicated in 21 CFR 314.70(d).

RESPONSIBILITIES**For All Applications**

- **The Office of New Drugs Regulatory Project Manager will:**
 - Compile and circulate the action package for review by the relevant review team members and the signatory authority before the regulatory action is taken, as described in the PROCEDURES section. In the case of a collaborative review (i.e., multiple office or division signatures on a single regulatory action letter) taken by more than one office or review division, the Office of New Drugs (OND) regulatory project manager (RPM) for the lead division will compile and circulate a single action package for review.²
 - Perform all other OND RPM activities listed in the PROCEDURES section.
- **The Chief, Project Management Staff will:**
 - Ensure that an action package is completed for all NDAs, BLAs, and applicable efficacy supplements
 - Ensure that the action package conforms to the content and format of an action package as described in the checklist
 - Ensure that, after an approval action, the package is forwarded by the OND RPM to the document room staff for further processing and archiving
- **The Reviewers³ will:**
 - Complete and file in the official archive their primary review of the application and any amendments that will be reviewed in the current review cycle in accordance with the DRG timeline for the application
- **The Discipline Team Leaders⁴ will:**
 - Ensure that all primary reviews for their respective disciplines are completed and filed in the official archive in accordance with the DRG timeline for the application.

² The lead review division is established between the parties involved in the review and regulatory action of the application or per MAPP 6020.5 *Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products*.

³ References to reviewers and team leaders throughout this MAPP include all disciplines on the review team (e.g., clinical, nonclinical toxicology, quality, biostatistics).

⁴ Ibid.

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- Sign off on the primary reviews in accordance with the DRG instructions. If the discipline team leader (DTL) does not concur with the primary review and the recommended regulatory action, the DTL will write a secondary review in accordance with the DRG instructions. This review should address any discrepancies between the DTL's and primary reviewer's recommendations and the rationale for the differences.

 - **The Cross-Discipline Team Leader will:**
 - Ensure that all discipline reviews are completed and filed in the official archive in accordance with the DRG timeline for the application

 - File in the official archive a cross-discipline team leader (CDTL) review in accordance with the DRG instructions

 - When also serving as the DTL:
 - Sign off on the primary review for his or her respective review discipline

 - Serve as the secondary reviewer for his or her respective discipline (i.e., the CDTL review will serve as the secondary review for the respective discipline)

 - **The Office of New Drugs Review Division Director or Deputy Director will:**
 - Ensure that all reviews are completed and filed in the official archive in accordance with the DRG timeline for the application

 - Write and file a review in the official archive in accordance with DRG instructions

 - Discuss his or her decision or recommendation with the CDTL and reviewers before archiving his or her review

 - Sign off on the action letter filed by the RPM in the official archive for applications where the division director is the signatory authority

 - **The Division Director(s) in the Office of New Drug Products and the Office of Biotechnology Products will:**
 - Ensure that reviews of chemistry, manufacturing, and controls information meet all applicable CDER policies and regulations and are completed and filed in the official archive in accordance with the DRG timeline for the application.

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- Determine the need for a tertiary review with OPQ offices. The need for a tertiary review will be based on quality risk and precedent and in many cases will not be necessary.
 - **All other Discipline Division Directors will:**
 - Ensure that reviews by their respective disciplines meet all applicable CDER policies and regulations and are completed and filed in the official archive in accordance with the DRG timeline for the application
 - Write and file in the official archive a brief review, when necessary, to resolve conflicts between primary and secondary reviewers or to integrate reviews completed by different primary reviewers or teams

For Applications Where the Office Director in One of the OND Offices Is the Signatory Authority

- **The Office's Associate Director for Regulatory Affairs will:**
 - Ensure that the action package and recommended regulatory action meet all applicable CDER policies and regulations
- **The Office Director or Deputy Director will:**
 - Write and file in the official archive a review that documents the decision for regulatory action and provides a rationale for concurrence or nonconcurrence with the review team and the division director
 - Share his or her review with the division director and review team leaders, as well as the reviewers when feasible, before finalizing the memo
 - Sign off on the action letter filed by the RPM in the official archive
- **The Associate Director for Pharmacology/Toxicology will:**
 - Ensure that reviews of nonclinical pharmacology/toxicology information meet all applicable CDER policies and regulations and are completed and filed in the official archive in accordance with the DRG timeline.
 - Write and file in the official archive a brief review for all new molecular entity (NME) NDAs and original BLAs. The review should address any complicated or controversial regulatory or scientific issues or outstanding issues.

For All Applications After Approval

- **The Document Room Staff will:**
 - Process final action packages according to the procedures and timelines described in the Document Processing Manual (GPR-016) *Processing Action Packages for NDAs and BLAs* and MAPP 4520.1 Rev. 1 *Communicating Drug Approval Information* (see also the PROCEDURES section)
 - **The Division of Information Disclosure Policy will:**
 - Perform a disclosure review of the final action package consistent with the established redaction prioritization scheme and timelines and procedures described in MAPP 4520.1 Rev. 1
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PROCEDURES**Manufacturing Facility Assessments⁵**

- Before taking a regulatory action on an original NDA or BLA, the Office of Process and Facilities (OPF) facility reviewer should, in coordination with the quality review team, document his or her facility assessment in the applicable review template and make an overall recommendation (i.e., approve, withhold) on the facilities in the electronic archive. Both the documented review and the recommendation in the electronic archive should be complete before an action is taken.
- For some NDA efficacy supplements with quality components, a manufacturing facility current good manufacturing practice assessment is required (e.g., a new strength; a manufacturing process or site change).
- For all BLA efficacy supplements, a manufacturing facility assessment must be performed.
- For an approval action, the OND RPM must confirm within 1 week before the action that the overall recommendation is acceptable.

⁵ See the POLICY section for additional information regarding overall recommendations and taking regulatory actions.

Compiling the Action Package

For all actions

- The OND RPM:
 - Must draft an appropriate action letter.
 - Must compile the action package in the order established by the checklist. Documents within each section of the action package should be arranged by date, with the most recent document located at the beginning of the section (i.e., reverse chronological order).
 - Should use tabs to differentiate sections of the package and insert a colored sheet of paper between multiple reviews or documents within a single section. Documents within the package should not be stapled.
 - Should indicate on the checklist the status of each item (e.g., not applicable, date of completed review). Comments may be added to the checklist to capture additional information. The checklist is cumulative and should be updated for each review cycle. The checklist should be placed at the beginning of the action package to serve as the table of contents.
 - Should mark as draft those documents that are still in draft form. Although action packages generally contain final documents (e.g., reviews, memos) when circulating for signatory review, some documents may be circulating in draft form only (e.g., checklist, action letter).

For approval actions

- The OND RPM must:
 - Within 1 week of the planned action date, confirm that there still is an acceptable establishment evaluation recommendation.
 - If a press communication has been prepared, notify the press office of the planned action date.
 - If applicable, ensure that a postmarketing requirement/postmarketing commitment development template for each postmarketing requirement/postmarketing commitment is completed and filed in the official archive according to MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

- For original NDAs and efficacy supplements, complete the exclusivity summary and file it in the official archive for signature by the division director.
- For original NDAs, BLAs, and efficacy supplements:
 - Request consent from each officer or employee of the FDA who participated in the decision to approve the application to include his or her name on the **Officer/Employee List** for posting on the Internet
 - Compile a list of officers and employees who consented to having their names included on the list

Circulating the Action Package

- The OND RPM:
 - Must circulate the action package for review through the appropriate review team members according to the timeline established in the DRG
 - Should deliver the action package to the division director (when the division director is the signatory authority) or to the associate director for regulatory affairs (when the office director is the signatory authority) for review according to the timeline established in the DRG

Taking a Regulatory Action

For complete response and tentative approval actions

- The OND RPM must:
 - Enter the final action letter in the official archive for sign-off by the signatory authority. For tentative approval actions, attach the agreed-upon labeling and REMS, if appropriate, to the letter.
 - Send a copy of the signed action letter to the applicant via fax or secure email and confirm receipt of the action letter with the applicant.
 - Ensure that all applicable documents, including the signed action letter, are included in the action package.
 - Complete the checklist and include a copy in the action package.

For approval actions

- The OND RPM:
 - For NDA 505(b)(2) applications, must:
 - Check the Approved Drug Products With Therapeutic Equivalence Evaluations (the Orange Book) for new patents and/or exclusivity (including pediatric exclusivity) that were listed after the application received 505(b)(2) clearance for the approval action. This activity should be performed approximately 3 to 4 weeks before the **targeted action date** and on the day of the action. If there are new patents and/or exclusivity, the RPM must consult with the 505(b)(2) Program Manager in the OND IO before taking an approval action.
 - Finalize and file the 505(b)(2) assessment in the official archive.
 - Must enter the final action letter in the official archive for sign-off by the signatory authority and:
 - Attach the final agreed-upon labeling text
 - Attach the final REMS and appended materials, if any
 - Must send a copy of the signed action letter to the applicant with its enclosures (i.e., final agreed-upon labeling text, REMS and appended materials) via fax or secure email and confirm receipt of the action letter with the applicant.
 - If a press communication has been prepared, must notify the press office as soon as receipt of the approval letter has been confirmed by the applicant.
 - Must ensure that all applicable documents, including the signed action letter, are included in the action package.
 - Must complete the checklist and file it in the official archive.
 - Within 1 business day of approval, must issue an email to the CDER-APPROVALS distribution list to notify personnel of the approval. If the application is for an NME or original BLA, the OND RPM should include the Center Director on the email. The email should include the following information:
 - NDA/BLA/supplement number
 - Product names (proprietary and established/proper names)
 - Applicant (not agent) name
 - Approval date

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- Chemical, review priority, and any other application classification codes
 - Indications
 - Route(s) of administration
 - Prescription or nonprescription (Rx or OTC)
- Should attach to the email the action letter with its enclosures and the summary review(s).

Processing and Archiving the Action Package

- Within 1 business day of approval, the RPM must email the following information to the CDER-DRTL-ALL distribution list:
 - Application number
 - NME or non-NME status
 - Number of action package volumes and their thickness in inches
 - Whether the pages are printed single- or double-sided
- The RPM must attach a printed copy of the email sent to CDER-DRTL-ALL to the outside cover of the action package.
- Within 2 business days of an approval action, the OND RPM must deliver the action package to the document room staff for scanning and archiving.
- The document room staff must do the following within 3 business days of receipt for NMEs and original BLAs, and within 5 business days of receipt for non-NME NDAs and efficacy supplements:
 - Scan the action package and insert PDF bookmarks within the action package
 - Perform a quality control check for scanning errors
 - File the bookmarked action package into the official electronic archive
 - Acknowledge completion of action package processing and archiving by responding to the OND RPM's original email notification, with a courtesy copy email to the DIDP
 - Attach a printed copy of the acknowledgment email to the cover of the paper action package and place the paper package on the OND RPM shelf in the document room
- Upon retrieval of the action package from the document room shelf, the RPM must archive the original action package according to division policy.

REFERENCES⁶

- Document Processing Manual (GPR-016) *Processing Action Packages for NDAs and BLAs*
- Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*
(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)
- MAPP 4151.1 Rev. 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*
- MAPP 4180.4 *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide*
- MAPP 4520.1 Rev. 1 *Communicating Drug Approval Information*
- MAPP 6010.8 Rev. 1 *NDAs and BLAs: Communication to Applicants of Planned Review Timelines*
- MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*
- MAPP 6020.5 *Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products*

DEFINITIONS

- **Action letter:** An approval, tentative approval, or complete response letter.
- **Action package:** A compilation of: (1) FDA-generated documents related to review of an NDA, BLA, or efficacy supplement; (2) documents pertaining to the format and content of the application generated during the drug development phase (investigational new drug application); (3) labeling submitted by the applicant and/or generated by the FDA; and (4) certain documents submitted by the applicant (e.g., REMS).

⁶ MAPPs can be found on the Manual of Policies and Procedures Web page at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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- **Action package checklist:** A list of documents included in, and administrative summary for, the action package. The template for this checklist is located in the CST electronic repository.
 - **Application:** An NDA, BLA, or efficacy supplement.
 - **Efficacy supplement:** A supplemental application proposing one of the following types of changes to the prescribing information that:
 - Adds or modifies an indication or claim.
 - Revises the dose or dose regimen.
 - Provides a new route of administration.
 - Makes a comparative efficacy claim naming another drug product.
 - Significantly alters the intended patient population.
 - Changes the marketing status from prescription to nonprescription use.
 - Provides for, or provides evidence of effectiveness necessary for, the traditional approval of a product originally approved under 21 CFR part 314, subpart H, or 21 CFR part 601, subpart E (accelerated approval).
 - Provides for, or provides evidence of effectiveness necessary for, the traditional approval of a product originally approved under 21 CFR part 314, subpart I, or 21 CFR part 601, subpart H (the animal rule).
 - Incorporates information based on at least one adequate and well-controlled clinical study. This includes labeling and manufacturing supplements requiring clinical data for approval.
 - **Final review:** A review that has been filed in the official archive with all required signatures.
 - **Officer/Employee List:** A list with the name of each officer or employee of the FDA who participated in the decision to approve the application and who consented to have his or her name included on the list.
 - **Part 3 combination product:** A combination product as defined in 21 CFR 3.2(e) comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.

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- **Summary review:** A documentation of the conclusions from all reviewing disciplines, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrency with review conclusions (see section 505(l)(2)(C)(iv) of the Federal Food, Drug, and Cosmetic Act). A number of reviews might, under various circumstances, be considered the summary review. In most cases, a single document will represent the summary review, but in some cases, more than one document may represent the summary review. For purposes of this MAPP, the summary review should be identified as follows.
 - The division director’s review supporting approval normally should be the summary review. However, the final determination of which review should be designated the summary review depends on which review best fits the statutory definition.
 - If the division director’s recommended regulatory action is a complete response but the office director’s decision is to approve, then both the office director’s and division director’s reviews should be considered summary reviews.
 - If an application has been through several review cycles and more than one summary review has been written, the review that discusses the approval decision should be considered the summary review for purposes of this instruction.
 - If the final review states the approval decision only, but the previous review(s) includes the discipline(s) findings and conclusions, both reviews should be considered the summary review.
 - **Targeted action date:** The date the review team intends to issue an action letter for a pending application. When such a date has not been identified, the targeted action 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 PDUFA or BsUFA and subsequent legislation reauthorizing those acts.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
6/13/16	Rev. 1	Updated to include information on the summary review, the 505(b)(2) clearance process, the NDA/BLA inspection process, and other changes to the approval and action package process implemented since 2002. Significant reorganization of the content.