
OFFICE OF GENERIC DRUGS

Requesting Methods Validation for Abbreviated New Drug Applications (ANDAs)

CONTENTS

PURPOSE
BACKGROUND
REFERENCES
DEFINITIONS
POLICY
RESPONSIBILITIES
PROCEDURES
EFFECTIVE DATE

PURPOSE

- To assist reviewers in defining when the Office of Generic Drugs (OGD) should request that analytical methods and testing procedures be validated by FDA laboratories when approving an ANDA.
 - To establish an OGD approval policy when laboratory results are pending.
-

BACKGROUND

- Since 1981, methods validation has not been an approval criterion for new drug applications (NDAs). Until 1997, however, OGD's policy was to require satisfactory methods validation prior to approval of abbreviated new drug applications (ANDAs) for non-compendial drug products. In some cases, ANDA approvals have been delayed pending completion of methods validation. Validation of the analytical methods and testing procedures remains an important component when ensuring drug product quality. However, there are circumstances where a delay in completion of the methods validation process is beyond the control of the applicant. In these instances, OGD wants to ensure that an application that is otherwise eligible for approval is

approved without undue delay. Therefore, OGD is revising its policy regarding methods validation for applications that have been recommended for approval.

REFERENCES

- 21 CFR 314.50(e): Samples and labeling
 - 21 CFR 314.70: Supplements and other changes to an approved application
 - Compliance Program on Preapproval Inspections CP7346.832
-

DEFINITIONS

- **Establishment Evaluation Request (EER)** - A request made to evaluate establishments listed in an application.
 - **Methods Validation** - The analytical process of actual use testing of the applicant's proposed regulatory method(s) in an FDA laboratory.
 - **Methods Verification** - The process of testing a compendial ANDA drug substance or drug product by compendial procedures in an FDA laboratory for purposes of ensuring compliance with compendial specifications and evaluating the appropriateness of a particular formulation for analysis by the compendial methods.
 - **Regulatory Methods** - The analytical procedures that are proposed by the applicant and agreed upon by the Agency to determine if the drug substance or drug product meets its established specifications. For drug substances and drug products having monographs in the USP, the USP analytical methods are considered regulatory by definition.
 - **USP** - Reference to the current edition of the *United States Pharmacopeia* and its supplements.
-

POLICY

- OGD does not require or request methods verification by an FDA laboratory of a product for which a USP monograph exists. However, FDA laboratories may conduct methods verification analyses of compendial products at their option. Application approval is not dependent on receipt of these test results. Proposals for alternate

analytical methods for products that are the subject of a USP monograph will be considered during the review process. There is no need for FDA laboratories to validate the alternate methods since the official methods for regulatory purposes are those of the USP and, therefore, OGD does not request methods validation for alternate methods for compendial products.

- If there is no USP monograph for a drug substance or drug product, the applicant's proposed regulatory analytical methods usually will be validated by an FDA laboratory.
- Under certain circumstances, methods validation for an ANDA for a non-compendial drug product may be waived. Waiver of methods validation for non-compendial drug products should be considered on a case-by-case basis. The final decision should be documented in the application. Circumstances that support a waiver should include but are not limited to:
 1. The proposed analytical methods have been validated previously in an FDA laboratory under another of the same applicant's ANDAs for a similar drug product (e.g., different strength, different packaging configuration).
 2. There exists in the compendium a monograph for a similar dosage form (e.g., For Injection vs. Injection), and the applicant's proposed regulatory methods are contained therein and the reviewer has verified that the change in dosage form will cause no analytical interferences in the compendial procedures. That is, the reviewer has determined that the suitability of the compendial methods under actual use conditions is verified.
- The chemistry team leader and the division director should sign off on an approval package if all aspects of the ANDA are complete and satisfactory, excluding methods validation, EER results, and/or office-level bioequivalence review.
- OGD should not wait for completion of methods validation for more than 30 days from the date the approval package is signed off by the chemistry team leader and is forwarded to the chemistry division director to begin the administrative review process.
- Following the lapse of the 30-day laboratory response period, the application should be approved if all other aspects of the ANDA, including the EER and office-level bioequivalence review, are satisfactory and the following criteria are met:
 1. There is no undue delay in sample submission by the applicant.

2. There is no apparent problem encountered with the validation in progress; or the validation has not been initiated by the servicing laboratory.
 3. There is a commitment from the applicant in the ANDA to resolve any problems with the methods validation.
- The 30-day laboratory response period does not apply to tentative approvals. Issuance of a tentative approval letter may occur without waiting for the 30-day clock to expire, unless there are known problems with the methods validation.
 - OGD should expect the applicant to provide samples to the servicing laboratory within 10 working days of the request and should consider longer time frames to be *undue delay*. OGD should not approve the application prior to the **completion** of the methods validation and the resolution of the deficiencies if it is determined there were delays in the provision of samples to the laboratory or if significant problems are identified in the course of methods validation.
 - Whether pre- or postapproval, the chemistry review branch should evaluate negative laboratory findings and determine their impact on the applicable submission.
-

RESPONSIBILITIES

Review Chemist

- Evaluates methods proposed in the application and completes appropriate review(s).
- Requests methods validation. (See PROCEDURES)
- Ensures that the applicant is aware that the USP methods are official for regulatory purposes for compendial ANDAs that propose alternate in-house methods.
- Evaluates evidence (e.g., placebo analysis) from the applicant that excipients in their particular formulation do not interfere with accurate analysis using the compendial methods, and ensures that applicants validate the compendial procedures for their stability indicating properties if they want to use the procedures in their stability programs.
- Communicates to the servicing laboratory any specific concerns with the analytical methods to be validated and with actions taken in the resolution of issues identified by the laboratory.

Chemistry Team Leader

- Signs off on the approval package if all aspects are found acceptable except for the absence of methods validation, EER results, and/or office-level bioequivalence endorsement.

Project Manager

- Determines that the firm has included a commitment to resolve any problems identified with the methods validation in the original submission, or ensures that the application is amended later to include this commitment.
- Monitors each application for completion of reviews and for receipt of results of methods validation. Facilitates preparation of the approval package.
- In the event that methods validation is incomplete, notes the date the chemistry team leader concurs with and signs off on the approval package (all components, except EER, methods validation, and/or office-level bioequivalence endorsement are ready for approval) to determine when the 30-day laboratory response period has elapsed.
- Notifies the servicing laboratory of the start date of the 30-day response period. Contacts the servicing laboratory at the conclusion of the 30-day period and documents the status of methods validation and determines if samples were submitted in a timely fashion. Recommends the appropriate processing of the pending application based on the criteria established above under Policy and reviewer's evaluation of the problems identified, if any.
- Maintains a database of applications approved with laboratory results still pending. Monitors these applications until the results are received at OGD, reviewed and found satisfactory by the chemist. Pertinent dates should be documented.

Regulatory Support Branch

- Notifies the appropriate FDA laboratory when a compendial application is received.
-

PROCEDURES

- A request for validation of the applicant's proposed regulatory analytical methods should be sent by the review chemist to the appropriate servicing laboratory using Form FDA 2871a. This action should be taken as soon as the need is identified and the test methods and specifications are determined to be adequate by the review chemist.

A methods validation request can be made before the Division of Bioequivalence has finalized the dissolution method and specifications. Unless there are known problems/changes at the time of the chemistry review, the dissolution method submitted by the firm should be validated by the laboratory. If there are subsequent changes, the review chemist should evaluate if an additional testing request should be made.

A copy of the methods, testing specifications, and composition statement should be included with the request. The package should be sent to the servicing laboratory via any express means with a receipt for tracking purposes.

- Requests should be processed and carried out as detailed in the Supplement to the Compliance Program on Preapproval Inspections CP7346.832.
- The chemistry/microbiology review should be part of the approval package along with the bioequivalence and labeling reviews. Upon concurrence by the chemistry team leader, the 30-day waiting period starts and the package should proceed through the final administrative review channels. If, after administrative review, the application remains approvable (including an acceptable EER and office-level bioequivalence endorsement), the project manager should determine the status of the methods validation process. The application should be approved with or without results of the methods validation at the end of the 30-day laboratory response period, except as noted below.
 1. There was an undue delay in sample submission by the applicant.
 2. There are problems identified in the course of methods validation by the servicing laboratory.
 3. There is no commitment from the applicant to resolve any problems subsequently found by the FDA laboratory.

Any problem identified with the method or the product should be evaluated by the review chemist for its significance. Any problem that potentially affects the quality of the drug product should be resolved prior to application approval.

- When approval is granted in the absence of a completed methods validation, the approval letter should be revised to include the following statement as the last paragraph:

Validation of the regulatory methods has not been completed. It is the general policy of the OGD not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

The revised approval letter should be endorsed by the chemistry reviewer and team leader as well as the division director.

- If laboratory results are received during this 30-day period and they reveal problems with the methods or the product, the approval of the application should be delayed and the results transmitted to the applicant. The applicant should be asked to address these issues as soon as possible in an amendment to the application. This amendment should be given priority review in consultation, if necessary, with the servicing laboratory. If the amended methods are satisfactory to OGD and they address the concerns of the laboratory, the application can then be approved, provided all other aspects of the application are acceptable. Out-of-specification results on products already expired at the time of testing should be evaluated for their significance and relevance. Any product failures should be satisfactorily resolved prior to application approval. Routine revalidation may be done after approval of the application.
 - Testing at a second FDA laboratory can be requested by the review chemist to resolve discrepant results obtained by an applicant and by the FDA servicing laboratory. The request must receive concurrence from the team leader and the division director.
 - For methods validation completed after an application is approved, any deficiencies identified should be communicated promptly to the applicant. Generally, the response addressing the deficiencies can be submitted as a changes-being-effected supplement.
 - If the methods validation is waived, this fact should be documented and filed in the ANDA.
-

EFFECTIVE DATE

This MAPP is effective upon date of publication.