OFFICE OF GENERIC DRUGS

Requesting Methods Validation for Abbreviated New Drug Applications

CONTENTS

PURPOSE

- This MAPP describes situations in which review chemists should request validation of analytical procedures by FDA laboratories for abbreviated new drug applications (ANDAs), and establishes the Office of Generic Drugs' (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 before approval of abbreviated new drug applications (ANDAs) for noncompendial drug products. In some cases, ANDA approvals were delayed pending completion of methods validation. Validation of the analytical methods and testing procedures was considered an important component when ensuring application approvability. However, there were circumstances when a delay in completion of the methods validation process was beyond the control of the applicant. In those instances, OGD wanted to ensure that an application that was otherwise eligible for approval was approved without undue delay. Therefore, in November 1998, OGD revised its policy regarding methods validation for applications that have been recommended for approval to allow approval of an ANDA if (1) there was no undue delay in sample submission by the applicant, (2) there is no apparent problem with the validation in progress or the validation has not been initiated by the servicing laboratory, and (3) there is a commitment from the applicant to resolve any problems with methods validation. Now, to better use the limited resources of the program to ensure adequacy of critical and/or complex methods, OGD has determined that there are other situations in which methods validation is not needed to support approval of ANDAs. Consequently, OGD is revising its policy regarding methods validation consistent with this determination.

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 proposed by the applicant and agreed upon by the Agency to determine whether 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:** The current edition of the *United States Pharmacopeia* and its supplements.

POLICY

- Methods validation requests will be limited to noncompendial drug products and, with team leader and division director (or deputy) concurrence, will be further subject to reviewer discretion because of specific concerns (i.e., for cause) relating to a drug product or an analytical method. Representative for cause examples include (but are not limited to):
  - New emerging analytical technologies
  - Analytical methods for novel/complex drug delivery systems (e.g., transdermal delivery system (TDS), metered-dose inhaler (MDI), nasal spray)
  - Chromatographic methods for quantitation of low dose drugs
  - Chromatographic methods for resolving multiple drug components with concomitant impurities/degradants

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

- If there is no USP monograph for a drug substance or drug product, the applicant's proposed regulatory analytical methods may be validated by an FDA laboratory.

- Under certain other circumstances, methods validation for an ANDA for a noncompendial drug product may clearly be waived. The final decision should be documented in the application. Circumstances that support a waiver include, but are not limited to:

    - 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).

    - There exists in the compendium a monograph for a similar dosage form (e.g., for injection vs. injection) containing the applicant's proposed regulatory methods, 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 verified the suitability of the compendial methods under actual use conditions.

- The division director will sign off on an approval package if all aspects of the ANDA are complete and satisfactory, excluding methods validation and EER results.

- OGD will not wait for completion of methods validation to begin the administrative review process.

- Upon completion of the administrative review process, the application will 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 methods validation.

- OGD expects the applicant to provide samples to the servicing laboratory within 10 working days of the request and will consider longer time frames to be *undue delay*. If it is determined that there were delays in the provision of samples to the laboratory, or if significant problems are identified in the course of methods validation, OGD will not approve

the application before the ***completion*** of the methods validation and the resolution of the deficiencies.

- Whether pre- or postapproval, the chemistry review branch will evaluate negative laboratory findings and determine their impact on the applicable submission.

RESPONSIBILITIES

The Review Chemist will:

- Evaluate methods proposed in the application and complete appropriate review(s).
- Request methods validation (see PROCEDURES).
- Ensure that the applicant is aware that the USP methods are official for regulatory purposes for compendial ANDAs that propose alternative in-house methods.
- Evaluate 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 ensure that applicants validate the compendial procedures for their stability-indicating properties if they want to use the procedures in their stability programs.
- Communicate 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.

The Chemistry Team Leader will:

- Sign 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, unless there is undue delay in sample submission by the applicant.

The Project Manager will:

- Determine that the firm has included a commitment to resolve any problems identified with the methods validation in the original submission, or ensure that the application is amended later to include this commitment.
- Monitor each application for completion of reviews and for receipt of methods validation results, and see that the approval package is prepared.
- Notify the servicing laboratory of ANDAs undergoing the administrative review process for approval, document the status of methods validation, and determine whether samples were submitted in a timely fashion.
- Recommend the appropriate processing of the pending application based on the criteria established above under Policy and the reviewer's evaluation of the problems identified, if any.
- Maintain a database of applications approved with laboratory results still pending.

- Monitor these applications until the results are received at OGD, reviewed, and found satisfactory by the chemist. Pertinent dates should be documented.

PROCEDURES

- A request for validation of the applicant's proposed regulatory analytical methods is sent by the review chemist to the Office of Regulatory Affairs (ORA) coordinator in the Division of Field Science (DFS) using form FDA 2871a. This action should be taken as soon as the need is identified and the test methods are determined to be adequate by the review chemist.

  A copy of the methods, testing specifications, and composition statement is to be included with the request. The package is sent to DFS by current procedures.

- Requests are processed and carried out as detailed in the Supplement to the Compliance Program on Preapproval Inspections CP7346.832.

- The chemistry/microbiology review is included in the approval package, along with the bioequivalence and labeling reviews. Upon concurrence by the chemistry team leader, the package proceeds 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 determines the status of the methods validation process. The application can be approved with or without results of the methods validation, except under the circumstances 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 is evaluated by the review chemist for its significance. Any problem that potentially affects the quality of the drug product must be resolved before application approval.

- When approval is granted in the absence of a completed methods validation, the approval letter is 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 approval letter is endorsed by the chemistry reviewer and team leader as well as the division director.

- If the laboratory results are received during the administrative review process for approval and they reveal problems with the methods or the product, the approval of the application is delayed and the results transmitted to the applicant. The applicant is asked to address these issues as soon as possible in an amendment to the application. This amendment is 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 are evaluated for their significance and relevance. Any product failures must be satisfactorily resolved before application approval. Routine revalidation can be done after approval of the application.

- The review chemist can request testing at a second FDA laboratory to resolve conflicting results obtained by an applicant and by the FDA servicing laboratory. The team leader and the division director must concur with the request.

- For methods validation completed after an application is approved, any deficiencies identified are 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 must be documented and filed in the ANDA.

EFFECTIVE DATE

This MAPP is effective upon date of publication.