

Analytical Procedures and Method Validation: Highlights of the FDA's Draft Guidance



Chemists in the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research review proposed analytical procedures submitted as part of new drug applications (NDAs) and abbreviated new drug applications (ANDAs). These procedures are subjected to validation in FDA laboratories. To facilitate the validation process and the generation of the information necessary for preparing a successful regulatory submission, FDA has updated the 1987 document, "Guideline for Submitting Samples and Analytical Data for Methods Validation." Although the draft guidance covers product license applications and biologics license applications, this article highlights its recommendations for NDAs and ANDAs.

The development of meaningful specifications is predicated upon the use of validated analytical procedures that can assess changes in a drug substance or drug product during its lifetime. Method validation is the process of demonstrating that analytical procedures are suitable for their intended use and that they support the identity, strength, quality, purity, and potency of the drug substances and drug products. The U.S. Food and Drug Administration (FDA) draft guidance document "Analytical Procedures and Methods Validation" describes the regulatory method validation process for drug substances and drug products covered by new drug applications (NDAs), abbreviated new drug applications (ANDAs), supplements to these applications, and drug master files (1). These applications must contain method validation information to support the adequacy of the analytical procedures. The draft guidance also serves as an update of the February 1987 "Guideline for Submitting Samples and Analytical Data for Methods Validation" (see the FDA web site <http://www.fda.gov/cder/guidance> for all guidances). The update reflects changes introduced by the International Conference on Harmonization of Technical Requirements for the Registration of Drugs for Human Use

(ICH) guidances, changes in technology, and current policy.

This article provides an overview of the governing paradigm, the guidance document, and the guidance development process that directed FDA's Center for Drug Evaluation and Research's Analytical Methods Technical Committee in this effort.

Background

The Center for Drug Evaluation and Research (CDER) is guided by the governing paradigm of *research to policy to review*, as presented in Figure 1. This evolving process allows guidances to be updated based upon advances in scientific knowledge, changes in regulatory requirements, and policy mandates. This process is supported by FDA's regulation on good guidance practices (2).

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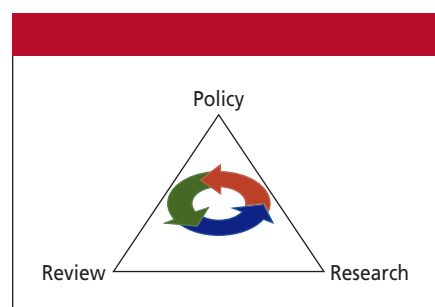


Figure 1: Research to policy to review. Description of the evolving regulatory process.

In a 7 March 1996 *Federal Register* notice, FDA provided the following definition for guidance documents (3):

The term *guidance documents* means

- documents prepared for FDA review staff and applicants relating to the processing, content, and evaluation of applications and relating to the design, production, manufacturing, and testing of regulated products;
- documents prepared for FDA personnel or the public that establish policies intended to achieve consistency in the agency's regulatory approach;
- documents that describe the agency's policy and regulatory approach to an issue; and
- documents that establish inspection and enforcement policies and procedures.

The good guidance practices (GGPs) explicitly state that when FDA is first communicating *new or different* regulatory expectations not readily apparent from the applicable statute or regulations to a broad public audience, the agency should follow officially designated guidance document procedures.

The draft guidance has been prepared to be consistent with the *ICH Q2A: Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology* guidances (4,5). It emphasizes the ICH recommendations for noncompendial analytical procedures and elaborates on topics such as types of analytical procedures, reference standard qualification and characterization, format of analytical procedures submitted in NDAs and ANDAs, validation of noncompendial analytical procedures, compendial analytical procedures, content and processing of validation packages, and revalidation.

The draft guidance discusses various methodologies including high performance liquid chromatography (HPLC), gas chromatography (GC), spectrophotometry, spectroscopy, capillary electrophoresis (CE), optical rotation, dissolution, and particle-size analysis. The treatment of instrument output and statistical analysis also are covered.

Types of Analytical Procedures

The draft guidance defines regulatory analytical and alternative analytical procedures and stability-indicating assays. Regulatory analytical procedures are of two types: compendial and noncompendial. The compendial analytical procedures in the *United States Pharmacopeial/National Formulary (USP 24/NF 19)* are those legally recognized

as the regulatory procedures for compendial items (6). These procedures, which are used for determining compliance with the Federal Food, Drug, and Cosmetic Act, section 501b, are statutory and legally enforceable. Noncompendial analytical procedures are submitted with the NDA or ANDA application.

Alternative analytical procedures may be proposed by applicants in place of regulatory analytical procedures. Generally, applicants attempt to use a compendial procedure, if one is available; however, in cases in which the compendial procedure is nonstability indicating or insufficiently specific for a particular drug product formulation (because of the presence of different excipients), an alternative procedure is warranted. In these cases, the alternative procedure requires complete validation data for its intended use; for example, release or stability testing. An alternative procedure also may be used in place of a noncompendial regulatory procedure in situations in which the regulatory procedure is stability indicating but the applicant has data showing that a nonstability-indicating procedure is acceptable for release testing. Another use of an alternative procedure might involve updating an old analytical procedure that is not stability indicating. In this case, one approach is to introduce the new stability-indicating procedure as an alternative procedure in the approved application and then follow the appropriate regulations and guidances to eventually replace the previous procedure with the new one.

An alternative procedure should provide the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

A stability-indicating assay is one that accurately quantitates the active ingredients without interference from degradation products, process impurities, excipients, or other potential impurities. Analytical procedures used for the assay of the drug substance alone or in the drug product in stability studies should be stability indicating.

Regulatory Approaches

The two major regulatory approaches — compendial and noncompendial procedures — are discussed below.

Compendial analytical procedures: The analytical procedures in the *USP 24/NF 19* are legally recognized under section 501(b) of the Federal Food, Drug, and Cosmetic Act as the regulatory analytical procedures for the compendial items. The suitability of

these procedures must be verified under actual conditions of use (7). When using *USP 24/NF 19* analytical procedures, the guidance recommends that information be provided for the following characteristics:

- specificity of the procedure,
- stability of the sample solution, and
- intermediate precision.

Compendial analytical procedures may not be stability indicating, and this concern must be addressed when developing a drug product specification because formulation-based interference may not be considered in the monograph specifications. Additional analytical tests for impurities or osmolality may be necessary to support the quality of the drug substance or drug product. In all cases, validated procedures should be used.

Noncompendial analytical procedures

and validation requirements: The most widely applied validation characteristics for noncompendial procedures are accuracy, precision (repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity, range, and robustness. *ICH Q2A* and *ICH Q2B*, as well as the reviewer guidance "Validation of Chromatographic Methods" (see <http://www.fda.gov/cder/guidance>), provide additional details about how these characteristics are validated. At the time of NDA and ANDA submissions to FDA, the applications should contain the above validation information to support the adequacy of the analytical procedures.

The validation of analytical procedures for drug substances and drug products requires that testing be performed by the applicants and acceptance criteria be proposed before regulatory evaluation by FDA laboratories can proceed. A discussion of the qualification and control of polymorphic and enantiomeric substances and the identification of organic impurities (further defined in *ICH Q3A: Impurities in New Drug Substances* [8]) may be necessary for drug substances.

In addition, the qualification and quantitation of inorganic impurities, residual solvents, possible isomers, and degradants (with associated stress studies) are recommended for regulatory assessment. Validation information for drug product analytical procedures should include topics such as degradation pathways for the drug substance in the dosage form, data that demonstrate the recovery from the sample matrix (dosage form), and data that demonstrate that freshly prepared or degraded excipients within the matrix do not interfere with the quantitation of the active ingredient. Other areas that should be addressed during drug product method validation include robust-

Table I: Validation characteristics of the various types of tests*

Type of Tests or Characteristics	Identification	Quantitative Testing for Impurities	Limit Testing for Impurities	Assay Dissolution (measurement only), Content-Potency	Specific Tests
Accuracy	—	+	—	+	+‡
Precision—repeatability	—	+	—	+	+‡
Precision—intermediate precision	—	+‡	—	+‡	+‡
Specificity	+§	+	+	+	+‡
Detection limit	—	—#	+	—	—
Quantitation limit	—	+	—	—	—
Linearity	—	+	—	+	—
Range	—	+	—	+	—
Robustness	—	+	—#	+	+‡

* — Signifies that this characteristic normally is not evaluated. + Signifies that this characteristic normally is evaluated.

‡ May not be needed in some cases.

‡ In cases where reproducibility has been performed, intermediate precision is not necessary.

§ Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.

|| Lack of specificity for an assay for release may be compensated for by impurity testing.

May be needed in some cases.

ness, stress studies, instrument output, and actual raw data.

The draft guidance has added a new category of *specific tests* for drug substances or products. Applicants may provide additional tests such as particle-size analysis, droplet distribution, and spray pattern tests and methodologies such as optical rotation,

differential scanning calorimetry, Raman spectroscopy, and X-ray diffraction techniques to control specific properties of the formulation or drug substance. Although all validation characteristics need not be documented, accuracy, precision, specificity, and robustness must be evaluated, where appropriate (see Table I).

Table I summarizes the validation characteristics that should be addressed during the validation of different types of analytical procedures. It should be noted that the same methodology can be used for more than one purpose. The validation information should support the intended purpose of the test. For example, if Raman spec-

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troscopy has been selected as the methodology to quantitate polymorphic forms as impurities or chiral HPLC has been selected to determine enantiomeric impurities, the recommended validation characteristics in Table I under quantitative testing for impurities would apply. However, if Raman spectroscopy or chiral HPLC were used for the purpose of identification or as specific tests, the recommended validation characteristics listed for those types of tests then would apply.

Reference Standards

Reference standards are a critical part of the regulatory method validation process. An official reference standard for many active ingredients can be obtained from the *USP 24/NF 19*. A reference standard used for regulatory purposes but not obtained from the *USP 24/NF 19* should be of the highest purity possible and be fully characterized. Characterization details of reference standards include approaches such as structural and physiochemical characterization and purity. Additional tests could include the evaluation of biological or immunochemical activity. A certificate of analysis that fully characterizes the standard should accom-

pany the standard. A working standard usually is an in-house standard that has been qualified against an official reference standard and again should be completely characterized. Full qualification and appropriate documentation are recommended for all nonofficial reference materials.

Method Validation Package: Contents and Processing

The draft guidance describes the FDA method validation process and the information recommended for inclusion in the method validation package in detail. Part of the method validation process may include FDA laboratory testing to demonstrate that the proposed procedures are suitable for regulatory and quality-control purposes. A method validation package and samples are needed for this process. Typically, one archival copy and two additional copies of the package are required. A tabular listing of all samples should be submitted along with the analytical procedures, validation data, analytical data (certificates of analysis), composition of the drug product, specification, and material safety data sheets.

On request from FDA, NDA or ANDA applicants may be required to submit sam-

ples of drug product, drug substance, impurities, noncompendial reference standards, and placebo (9). FDA laboratories will analyze the samples according to the submitted procedures to determine if the procedures are suitable for both regulatory and quality-control purposes. The laboratories will forward these results and comments to review chemists upon completion of the laboratory studies. FDA MaPP 5221.1: "Requesting Methods Validation for ANDAs" (see <http://www.fda.gov>) allows for an approval decision for ANDAs to proceed in the absence of completion of the method validation process, similar to the 1981 policy for new drugs (10).

Method Validation Problems and Delays

Some common problems can delay the successful validation of the methods by FDA laboratories. These include failure to

- provide a sample of a critical impurity, degradation product, internal standard, or novel reagent;
- submit well-characterized reference standards for noncompendial drugs;
- provide sufficient detail or procedures such as the use of arbitrary arithmetical

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corrections, failure to include system-suitability tests, and using different content uniformity and assay procedures for which equivalence factors have not been established;

- submit legible data such as appropriate instrument output with axes identified;
- appropriately ship samples to the FDA laboratories (for example, missing labels, poor packaging of samples, inadequate shipping forms, or missing customs forms for samples from outside the United States); and
- describe the proper storage conditions on shipping labels.

The most common cause of delay in FDA method validation study is that some or all of the needed samples are missing.

Additional Methodologies

Advances in technology ensure that novel methodologies will become available for regulatory science. The draft guidance highlights specific operating parameters that should be addressed during method development and validation, regardless of the chosen technology. Although HPLC and GC currently play a predominant role in assay procedures, emerging technologies such as CE and near-IR spectroscopy may play increasingly important roles in regulatory science. The draft guidance also provides details of the recommended parameters for the evaluation of CE, particle-size analysis, spectrophotometry, spectroscopy, optical rotation, and dissolution measurement.

Summary

This draft guidance, when finalized, will assist applicants in preparing comprehensive and successful regulatory submissions to support the method validation section of the chemistry, manufacturing, and controls portion of NDAs and ANDAs.

For Additional Reading

Readers who would like more information about analytical procedures and method validation can find information in several sources. The FDA and ICH guidances are available on the Internet at <http://www.fda.gov/cder/guidance>. The *United States Pharmacopeia 24/National Formulary* also provides information about compendial standards (7). Another source is "Guidance for Industry: Analytical Procedures and Methods Validation" (1).

FDA publications include the reviewer guidance document "Validation of Chromatographic Methods" and FDA CDER

MaPP 5221.1 "Requesting Methods Validation for ANDAs." Two useful publications are "The FDA Regulatory Methods Validation Program for New and Abbreviated New Drug Applications," (11) and "Regulatory Perspectives on Analytical Procedures and Methods Validation for Drug Substances and Drug Products" (12).

The International Conference on Harmonization of Technical Requirements for the Registration of Drugs for Human Use (Geneva, Switzerland) also has published several guidances. These include *ICH Q1A: Stability Testing of New Drug Substances and Products* (November 1994); *ICH Q1B: Photostability Testing of New Drug Substances and Products* (November 1996); *ICH Q1C: Stability Testing for New Dosage Forms* (May 1997); *ICH Q2A: Text on Validation of Analytical Procedures* (March 1995); *ICH Q2B: Validation of Analytical Procedures: Methodology* (May 1997); *ICH Q3A: Impurities in New Drug Substances* (January 1996); *ICH Q3B: Impurities in New Drug Products* (May 1997); *ICH Q3C: Impurities: Residual Solvents* (December 1997); *ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996); *ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (Draft Step 2) (November 1997); and *ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (March 1999).

References

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