Guidance for Industry

Analytical Procedures and Methods Validation

Chemistry, Manufacturing, and Controls Documentation

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2000
CMC #

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Guidance for Industry[1]

Analytical Procedures and Methods Validation

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- **!** *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed change.*
- **!** *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- **!** *If possible, e-mail an electronic copy (Word or WordPerfect) of the comments you have submitted to the docket to cunninghamp@cder.fda.gov.*

I. INTRODUCTION

This guidance provides recommendations to applicants on submitting analytical procedures,[2] validation data, and samples to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.[3] This guidance is intended to assist applicants in assembling information, submitting samples, and presenting data to support analytical methodologies. The recommendations apply to drug substances and drug products covered in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), product license applications (PLAs), and supplements to these applications.[4] The principles also apply to drug substances and drug products covered in Type II drug master files (DMFs). If a different approach is

[1] This guidance has been prepared by the Analytical Methods Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] *Analytical procedure* is interchangeable with *method* or *test procedure*.

[3] The terms *drug substance* and *drug product*, as used in this guidance, refer to human drugs and biologics.

[4] Sponsors preparing investigational new drug applications (INDs) should also consider the recommendations in this guidance. However, the amount and depth of the information that should be submitted to support an IND depends in large part on the phase of the investigation and the specific testing proposed in humans (see section V).

chosen, the applicant is encouraged to discuss the matter in advance with the center with product jurisdiction to prevent the expenditure of resources on preparing a submission that may later be determined to be unacceptable.

The principles of methods validation described in this guidance apply to all types of analytical procedures. However, the specific recommendations in this guidance may not be applicable to certain unique analytical procedures for products such as biological, biotechnological, botanical, or radiopharmaceutical drugs. For example, many bioassays are based on animal challenge models, immunogenicity assessments, or other immunoassays that have unique features that should be considered when submitting analytical procedure and methods validation information. Furthermore, specific recommendations for biological and immunochemical tests that may be necessary for characterization and quality control of many drug substances and drug products are beyond the scope of this guidance document. Although this guidance does not specifically address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products, validated analytical procedures should be used to analyze these materials. For questions on appropriate validation approaches for analytical procedures or submission of information not addressed in this guidance, applicants should consult with the appropriate chemistry review staff at FDA.

This guidance, when finalized, will replace the FDA guidance for industry on *Submitting Samples and Analytical Data for Methods Validation* (February 1987).

II. BACKGROUND

Each NDA and ANDA must include the analytical procedures necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product, including bioavailability of the drug product (21 CFR 314.50(d)(1) and 314.94(a)(9)(i)). Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 211.165(e) and 211.194(a)(2)).

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. The methods validation process for analytical procedures begins with the planned and systematic collection by the applicant of the validation data to support the analytical procedures. The review chemist evaluates the analytical procedures and validation data submitted in the NDA or ANDA. On request from FDA, an NDA or ANDA applicant must submit samples of drug product, drug substance, noncompendial reference standards, and blanks so that the applicant=s drug substance and drug product analytical procedures can be evaluated by FDA laboratories (21 CFR 314.50(e) and 314.94(a)(10)). The FDA laboratory analysis demonstrates that the analytical procedures are reproducible by laboratory testing. The review chemists and laboratory analysts determine the suitability of the analytical procedures for regulatory purposes. FDA investigators inspect the analytical laboratory testing sites to ensure that the analytical procedures used for release and stability

testing comply with current good manufacturing practices (CGMPs) (21 CFR part 211) or good laboratory practices (GLPs) (21 CFR part 58), as appropriate.

Each BLA and PLA must include a full description of the manufacturing methods, including analytical procedures, that demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency (21 CFR 601.2(a) and 601.2(c)(1)(iv)). Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 211.194(a)(2)). For BLAs, PLAs, and their supplements, the analytical procedures and their validation are submitted as part of the license application or supplement and are evaluated by the review committee. Representative samples of the product must be submitted and summaries of results of tests performed on the lots represented by the submitted sample must be provided (21 CFR 601.2(a) and 601.2(c)(1)(vi)). The review committee chair may request analytical testing by CBER laboratory analysts to evaluate the applicant=s analytical procedures and verify the test results.

All analytical procedures are of equal importance from a validation perspective. In general, validated analytical procedures should be used, irrespective of whether they are for in-process, release, acceptance, or stability testing. Each quantitative analytical procedure should be designed to minimize assay variation.

Analytical procedures and validation data are submitted in the sections of the application on analytical procedures and controls. Recommendations on information to be submitted are included in sections III through IX and XI of this guidance. Information on submission of the *methods validation package* to the NDA or ANDA and samples to the FDA laboratories is provided in section X.

III. TYPES OF ANALYTICAL PROCEDURES

A. Regulatory Analytical Procedure

A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the *U.S. Pharmacopeia/National Formulary* (USP/NF) are those legally recognized under section 501(b) of the Food, Drug, and Cosmetic Act (the Act) as the regulatory analytical procedures for compendial items. For purposes of determining compliance with the Act, the regulatory analytical procedure is used.

B. Alternative Analytical Procedure

An *alternative analytical procedure* is an analytical procedure proposed by the applicant for use instead of the regulatory analytical procedure. A validated alternative analytical procedure should be submitted only if it is shown to perform equal to or better than the regulatory analytical procedure. If an alternative analytical procedure is submitted, the applicant should provide a rationale for its inclusion and identify its use (e.g., release, stability testing), validation

data, and comparative data to the regulatory analytical procedure.

C. Stability-Indicating Assay

A *stability-indicating assay* is a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product. A stability-indicating assay accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities. If an applicant submits a non-stability-indicating analytical procedure for release testing, then an analytical procedure capable of qualitatively and quantitatively monitoring the impurities, including degradation products, should complement it. Assay analytical procedures for stability studies should be stability-indicating, unless scientifically justified.

IV. REFERENCE STANDARDS

A. Types of Standards

A *reference standard* (i.e., primary standard) may be obtained from the USP/NF or other official sources (e.g., CBER, 21 CFR 610.20). If there are questions on whether a source of a standard would be considered by FDA to be an official source, applicants should contact the appropriate chemistry review staff. When there is no official source, a reference standard should be of the highest possible purity and be fully characterized.

A *working standard* (i.e., in-house or secondary standard) is a standard that is qualified against and used instead of the reference standard.

B. Certificate of Analysis

A certificate of analysis (COA) for reference standards from non-official sources should be submitted in the section of the application on analytical procedures and controls. For standards from official sources, the user should ensure the suitability of the reference standard. The standard should be stored correctly and used within the established use interval.

C. Characterization of a Reference Standard

Reference standards from USP/NF and other official sources do not require further characterization. A reference standard that is not obtained from an official source should be of the highest purity that can be obtained by reasonable effort, and it should be thoroughly characterized to ensure its identity, strength, quality, purity, and potency. The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than, those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product. Analytical procedures used to

characterize a reference standard should not rely solely on comparison testing to a previously designated reference standard.

Generally, this characterization information should include:

- A brief description of the manufacture of the reference standard, if the manufacturing process differs from that of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described.

- Legible reproductions of the relevant spectra, chromatograms, thin-layer chromatogram (TLC) photographs or reproductions, and other appropriate instrumental recordings.

- Data establishing purity. The data should be obtained by using appropriate tests, such as TLC, gas chromatography (GC), high-pressure liquid chromatography (HPLC), phase solubility analysis, appropriate thermometric analytical procedures, and others as necessary.

- Appropriate chemical attribute information, such as structural formula, empirical formula, and molecular weight. Information to substantiate the proof of structure should include appropriate analytical tests, such as elemental analysis, infrared spectrophotometry (IR), ultraviolet spectrophotometry (UV), nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS), as well as applicable functional group analysis. Detailed interpretation of the test data in support of the claimed structure should be provided.

- A physical description of the material, including its color and physical form.

- Appropriate physical constants such as melting range, boiling range, refractive index, dissociation constants (pK values), and optical rotation.

- A detailed description of the analytical procedures used to characterize the reference standard.

For biotechnological/biological product reference standards, the recommendations on characterization information above may apply and should be considered. However, additional and/or different tests would be important to assess physicochemical characteristics, structural characteristics, biological activity, and/or immunochemical activity. Physicochemical determinations may include isoform, electrophoretic, and liquid chromatographic patterns, as well as spectroscopic profiles. Structural characterization may include a determination of amino acid sequence, amino acid composition, peptide map, and carbohydrate structure. Biological and/or immunochemical activity should be assessed using the same analytical procedures used to determine product potency. These can include animal-based, cell culture-

based, biochemical, or ligand/receptor-binding assays. While these tests may be needed for complete characterization of certain reference standards, specific recommendations for validation of biological and immunochemical tests are not contained in this guidance document.

V. METHODS VALIDATION FOR INDs

For an investigational new drug, sufficient information is required in each phase of an investigation to ensure proper identification, quality, purity, strength, and/or potency. The amount of information on analytical procedures and methods validation necessary will vary with the phase of the investigation (21 CFR 312.23(a)(7)).

For general guidance on analytical procedures and methods validation information to be submitted for phase 1 studies, sponsors should refer to the FDA guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995). General guidance regarding analytical procedures and methods validation information to be submitted for phase 2 or phase 3 studies will be provided in the FDA guidance for industry *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format,* when finalized (draft guidance published April 1999).

All analytical procedures should be fully developed and validation completed when the NDA, ANDA, BLA, or PLA is submitted.

VI. CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs

Any analytical procedure submitted in an NDA, ANDA, BLA, or PLA should be described in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results comparable to the applicant=s. Aspects of the analytical procedure that require special attention should be described. If the analytical procedure used is in the current revision of the USP/NF or other FDA recognized standard references (e.g., AOAC International *Book Of Methods*) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference may be provided rather than a description of the method (21 CFR 211.194). A description of analytical procedures from any other published sources should be provided, because the referenced sources may not be readily accessible to the reviewer.

The following is a list of information that should typically be included in a description of an analytical procedure.

A. Principle

A statement of the principle of the analytical procedure should be included. For example, separation is based on isocratic reversed phase HPLC with detection by UV.

B. Sampling

The number of samples (e.g., vials, tablets) selected, how they are used (i.e., as individual or composite samples), and the number of replicate analyses per sample should be described.

C. Equipment and Equipment Parameters

A listing of all equipment (e.g., instrument type, detector, column type, dimensions) should be included, as well as a list of equipment parameters (e.g., flow rate, temperatures, run time, wavelength settings). A drawing representing the experimental configuration (e.g., illustrating positions for a spray pattern analytical procedure) should be provided, when appropriate.

D. Reagents

A list of reagents and their grades (e.g., USP/NF, American Chemical Society (ACS) Analytical Reagent) should be included. If in-house or modified commercial reagents are used, directions for their preparation should be included. Unstable or potentially hazardous reagents should be identified, and storage conditions, directions for safe use, and usable shelf life for these reagents should be specified.

E. System Suitability Testing

System suitability test parameters and acceptance criteria are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integrated system. System suitability testing ensures that the system is working properly at the time of analysis. Appropriate system suitability criteria should be defined and included in the analytical procedure.

All chromatographic analytical procedures should include system suitability testing and criteria. Parameters typically used in system suitability evaluations are defined and discussed in the CDER reviewer guidance on *Validation of Chromatographic Methods* (November 1994).

System suitability testing is recommended as a component of any analytical procedure, not just those that involve chromatographic techniques. Regardless of the type of analytical procedure, testing should be used to confirm that the system will function correctly independent of the environmental conditions. For example, titration analytical procedures should always include the evaluation of a blank (commonly referred to as a *blank titration*).

F. Preparation of Standards

Procedures for the preparation of all standard solutions (e.g., stock, working standard solutions, internal standards) should be included.

G. Preparation of Samples

Sample preparation for individual tests should be clearly described. Specific details should be provided for unusual sample preparations (e.g., solid-phase extraction, derivatization).

H. Procedure

A step-by-step description of the procedure should be provided. The description should include, where appropriate, equilibration times, injection sampling sequence, and system suitability or start-up parameters. Unusual hazards should be identified.

I. Calculations

Representative calculations, with a tabulation defining all symbols and numerical factors, and specific instructions for the calculation of degradation products and impurities should be included. Any mathematical transformations or formulas used in data analysis should be described in detail. These may include logarithmic transformations used to obtain a linear relationship from exponential data, or the use of multiple order regression analyses.

J. Reporting of Results

1. General

The format used to report results (e.g., percent label claim, weight/weight, weight/volume, parts per million (ppm)) including the specific number of significant figures to be reported should be provided.

2. Impurities Analytical Procedures

The name and location/identifier (e.g., retention time (RT), relative retention time (RRT)) of impurities and the type of impurity (e.g., process, degradant, excipient degradant) should be included in the analytical procedures for impurities in the drug substance and drug product. The detection limit (DL) or quantitation limit (QL) should be stated, as appropriate. The DL or QL can be set using the drug substance's detection response.

Reporting of organic impurities should cover (1) specified identified impurities by name, (2) specified unidentified impurities by location/identifier, (3) any unspecified impurities, and (4) total impurities. The total organic impurities for the drug product or

drug substance is the sum of all impurities equal to or greater than their individual QL. See recommendations regarding appropriate QLs in FDA impurities guidances (see references). Inorganic impurities and residual solvents should also be addressed.

For the drug product, drug substance process impurities may be excluded from reporting if an acceptable rationale is provided in the sections on analytical procedures and controls. Drug product impurities from the drug product manufacturing process, packaging, and labeling should be addressed.

The above reporting information may not be strictly applicable to all products (e.g., biological, biotechnological, botanical, radiopharmaceutical drugs), but any significant process and product-related impurities should be determined and reported.

VII. METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs

A. Noncompendial Analytical Procedures

In an NDA, ANDA, BLA, or PLA, data must be submitted to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability (21 CFR 211.194(a)(2)). *Methods validation* is the process of demonstrating that analytical procedures are suitable for their intended use. At the time of submission, the NDA, ANDA, BLA, or PLA should contain methods validation information to support the adequacy of the analytical procedures.

The International Conference on Harmonisation (ICH) guidance *Q2A Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996) provide recommendations on validation of analytical procedures. Analytical procedures outside the scope of the ICH guidances should still be validated.

1. Validation Characteristics

Applicants should submit information on the validation characteristics of their proposed analytical procedures (see ICH *Q2A* and ICH *Q2B*). Although not all of the validation characteristics are needed for all types of tests (see section VII.A.3), typical validation characteristics are:

- Accuracy
- Precision (repeatability and intermediate precision)
- Specificity
- Detection limit
- Quantitation limit

- Linearity
- Range
- Robustness

2. Other Methods Validation Information

Methods validation information should also include:

- Data to demonstrate the stability of all analytical sample preparations through the time required to complete the analysis.

- Legible reproductions of representative instrument output or recordings (e.g., chromatograms) and raw data output (e.g., integrated areas), as appropriate. Instrument output for placebo, standard, and sample should also be provided (see section VII.A.2.c).

- Representative calculations using submitted raw data, to show how the impurities in drug substance are calculated.

- Information from stress studies (see section VII.A.2.b).

- Impurities labeled with their names and location identifiers (e.g., RRT for chromatographic data) for the impurity analytical procedure.

- For drug substances:

  - A discussion of the possible formation and control of polymorphic and enantiomeric substances.

  - Identification and characterization of each organic impurity, as appropriate. This information may not be needed for all products (e.g., botanicals). Other impurities (e.g., inorganics, residual solvents) should be addressed and quantitated.

    Recommendations on submitting information on impurities is provided in various FDA guidances such as the ICH guidance *Q3A Impurities in New Drug Substances* (January 1996).

  - A list of known impurities, with structure if available, including process impurities, degradants, and possible isomers.

- For drug products:

- A degradation pathway for the drug substance in the dosage form, where possible.

- Data demonstrating recovery from the sample matrix as illustrated by the accuracy studies.

- Data demonstrating that neither the freshly prepared nor the degraded placebo interferes with the quantitation of the active ingredient.

ICH *Q2A* and *Q2B* address almost all of the validation parameters. Areas that should be provided in more detail are described below.

a. Robustness

Robustness, a measure of the analytical procedure's capability to remain unaffected by small but deliberate variations, is described in ICH *Q2A* and *Q2B*. Such testing should be performed during development of the analytical procedure and the data discussed and/or submitted. In cases where an effect is observed, representative instrument output (e.g., chromatograms) should be submitted.

b. Stress Studies

Degradation information obtained from *stress studies* (e.g., products of acid and base hydrolysis, thermal degradation, photolysis, oxidation) for the drug substance and for the active ingredient in the drug product should be provided to demonstrate the specificity of the assay and analytical procedures for impurities**.** The stress studies should demonstrate that impurities and degradants from the active ingredient and drug product excipients do not interfere with the quantitation of the active ingredient. Stress studies are described in various FDA guidances relating to the stability of drug products (see references).

The design of the stress studies and the results should be submitted to the stability section of the application. Representative instrument output (e.g., chromatograms) and/or other appropriate data (e.g., degradation information obtained from stress studies) should be submitted in the sections on analytical procedures and controls.

c. Instrument Output/Raw Data

i. Organic Impurities

Representative data should be submitted to support an assessment of the organic impurities. Representative data for residual solvents are generally not needed. Instrument output and the raw numerical values (e.g., peak area)

with appropriate identification and labeling (e.g., RT for chromatographic peaks, chemical shift (δ) and coupling constant (J) for NMR) should be provided. The impurity profile should be assessed at the quantitation limit and the instrument output provided. Additional information should be provided to confirm that the impurity profile is adequately characterized. For example, a representative chromatogram using detection at a low wavelength, such as 205 nm, and double the proposed total run time could be submitted to support the specificity of the analytical procedure.

For quantitation purposes, the response factor of the drug substance may be used for impurities without a reference standard. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities often are based on analytical assumptions (e.g., equivalent detector response). Assumptions should be discussed and justified.

ii. Drug Substance

Data should be submitted showing the separation and detection of impurities using spiked or stress samples. Complete impurity profiles as graphic output (e.g., chromatograms) and raw data (e.g, integrated peak areas) of representative batches should be submitted in the sections on analytical procedures and controls for the drug substance. For ANDAs and related submissions, appropriate information for the batches used in the biobatch or submission batch should be provided. All responses (e.g., peaks) should be labeled.

The analytical procedure used should be capable of differentiating changes, if any, between past and present batches. The quantitation limit and the type of organic impurity (e.g., degradant, process impurity) should be stated. The analytical procedure number, batch number, manufacturing date and site, and date of analysis should be provided.

iii. Drug Product

Information such as instrument output (e.g., chromatograms) and raw data (e.g., integrated peak areas) from representative batches under long-term and accelerated stability conditions, and stressed samples should be submitted in the sections on analytical procedures and controls of the drug product. For ANDAs and related submissions, appropriate information for the biobatch or submission batch should be provided. References to the raw data (e.g., chromatograms) should be included in the stability section of the application.

At a minimum, the submission should include instrument output and raw data for release testing and at the latest available time point for the same batch. All responses (e.g., peaks) should be labeled and identified. In addition, the analytical procedure number, batch number of the drug product, manufacturing date, date of analysis, source and batch number of drug substance, manufacturing site, and container/closure information should be provided. The analytical procedures used should be capable of differentiating changes, if any, between past and present batches. The quantitation limit and the type (e.g., degradant, leachables from packaging) should be reported. Multiple methodologies can be used.

If process impurities from the drug substance and excipients with their related impurities are not reported in the impurities analytical procedure, the potential locations/identifier (e.g., RT, RRT) of these compounds should be described and listed in the analytical procedure.

3. Recommended Validation Characteristics for Types of Tests

Table 1 is a summary of the validation characteristics that should be addressed during validation of different types of analytical procedures. The same methodology can be used for several purposes. The validation information should support the intended purpose of the test. For example, if Raman spectroscopy is the methodology selected to quantitate polymorphic forms as impurities, or chiral HPLC for enantiomeric impurities, the recommended validation characteristics in Table 1 under *quantitative testing for impurities* would apply. However, if Raman spectroscopy or chiral HPLC are used for the purpose of identification or as specific tests, the recommended validation characteristics listed for those types of tests would apply.

Table 1. Recommended Validation Characteristics of the Various Types of Tests.

Type of Tests / Characteristics	Identification	Testing for Impurities		Assay Dissolution (Measurement Only), Content/Potency	Specific Tests
		Quantitative	Limit		
Accuracy	-	+	-	+	+[4]
Precision-Repeatability	-	+	-	+	+[4]
Precision-Intermediate Precision	-	+[1]	-	+[1]	+[4]
Specificity	+[2]	+	+	+[5]	+[4]
Detection Limit	-	-[3]	+	-	-
Quantitation Limit	-	+	-	-	-
Linearity	-	+	-	+	-
Range	-	+	-	+	-
Robustness	-	+	-[3]	+	+[4]

NOTE:

- \- Signifies that this characteristic is not normally evaluated.
- \+ Signifies that this characteristic is normally evaluated.
- 1 In cases where reproducibility has been performed, intermediate precision is not needed.
- 2 Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.
- 3 May be needed in some cases.
- 4 May not be needed in some cases.
- 5 Lack of specificity for an assay for release may be compensated for by impurities testing.

a. Identification

Identification analytical procedures may include tests such as IR, differential scanning calorimetry (DSC), X-ray diffraction (XRD), UV, and HPLC retention time. A specific identification test should be included for the active ingredient whenever possible. In cases where a nonspecific identification analytical procedure is proposed for the active ingredient, two independent analytical procedures are generally sufficient, if justified. For other identification tests (e.g., a chiral HPLC retention time as confirmation for the presence of an enantiomer, chloride test for a counterion) a single test is acceptable. This concept of the number of identification tests is

applicable to both the drug substance and drug product.

b. Impurities

The validation characteristics under *quantitative testing for impurities,* as described in Table 1, apply, regardless of which methodology is used to quantitate impurities. If the same analytical procedure is proposed as a limit test, validation characteristics under *limit testing for impurities* will apply.

c. Assay

Assay includes the content of the active ingredient, preservative (if used), and measurement of content in dissolution and content uniformity samples.

d. Specific Tests

Specific tests to control the drug substance, excipient, or drug product can include tests such as particle size analysis, droplet distribution, spray pattern, dissolution (excludes measurement), optical rotation, and methodologies such as DSC, XRD, and Raman spectroscopy. The validation characteristics may differ for the various analytical procedures. For example, accuracy, repeatability, intermediate precision and robustness should be evaluated for molecular size distribution gel permeation chromatography (GPC).

B. Compendial Analytical Procedures

The suitability of a compendial analytical procedure must be verified under actual conditions of use (21 CFR 211.194(a)(2)). Information to demonstrate that USP/NF analytical procedures are suitable for the drug product or drug substance should be included in the submission. Information on the specificity, intermediate precision, and stability of the sample solution should be included. Compendial assay analytical procedures may not be stability-indicating, and this should be considered when developing the specification (see section III.C). For compendial items, additional analytical procedures, such as impurities or osmolality, may be requested to support the quality of the drug product or drug substance. These additional analytical procedures should be validated (see section VII.A).

VIII. STATISTICAL ANALYSIS

A. General

Methods validation includes an assessment of the adequacy of the analytical procedure. Statistical analysis (e.g., linear regression analysis, relative standard deviation) of methods

validation data is often used to demonstrate the validity of the method. The statistical procedures for the analysis of the validation data should be determined prior to the start of any validation study. The procedure followed, including the amount of data to collect and the criteria used in determining the acceptability of the analytical procedure, should be specified.

The raw methods validation data and statistical procedures used to analyze the raw data should be provided and discussed in the sections on analytical procedures and controls. All statistical procedures used in the analysis of the data should be based on sound principles and be suitable for evaluating the dataset.

B. Comparative Studies

Comparative studies are performed to evaluate intermediate precision (e.g., different equipment, analysts, days). Comparative studies are also used to evaluate *between laboratory* variability (i.e., reproducibility) when an analytical procedure is used in more than one laboratory or to compare and evaluate the precision and accuracy of two analytical procedures (e.g., regulatory analytical procedure and an alternative analytical procedure). When comparative studies are performed, homogeneous samples from the same batch should be used, if feasible. Comparative results should be statistically analyzed and discussed and any bias explained.

C. Statistics

For information on statistical techniques used in making comparisons, as well as other general information on the interpretation and treatment of analytical data, appropriate literature or texts should be consulted (see references) .

IX. REVALIDATION

When sponsors make changes in the analytical procedure, drug substance (e.g., route of synthesis), or drug product (e.g., composition), the changes may necessitate revalidation of the analytical procedures. Revalidation should be performed to ensure that the analytical procedure maintains its characteristics (e.g., specificity) and to demonstrate that the analytical procedure continues to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product, and the bioavailability of the drug product. The degree of revalidation depends on the nature of the change. When a different regulatory analytical procedure is substituted (e.g., HPLC for titration), the new procedure should be validated (see section VII).

If during each use an analytical procedure can meet the established system suitability requirements only with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be reevaluated, amended, and revalidated, as appropriate.

FDA intends to provide guidance in the future on postapproval changes in analytical procedures.

X. METHODS VALIDATION PACKAGE: CONTENTS AND PROCESSING

Part of the methods validation process may include FDA laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A methods validation package (see X.A) and samples (see X.B) will be needed for this process.

A. Methods Validation Package

The methods validation package will usually include information copied from pertinent sections of the application. To aid the review chemist, these copies should retain the original pagination of the application sections.

For ANDA and NDA products, the archival copy and extra copies of the methods validation packages should be submitted with the application. For ANDAs and related supplemental applications, one archival copy and two extra copies of the methods validation package should be submitted. For NDAs and related supplemental applications, one archival copy and three extra copies should be submitted. For BLAs and PLAs, a separate methods validation package need not be submitted. Information similar to that specified here should be included in the BLA or PLA submission.

The methods validation package should include:

1. Tabular List of All Samples to Be Submitted

The list should include the lot number, identity (with chemical name and structure where required for clarity), package type and size, date of manufacture, and quantity of the samples.

2. Analytical Procedures

A detailed description of each of the analytical procedures listed in the specifications should be submitted. The description should be sufficient to allow the FDA laboratory analysts to perform the analytical procedure (see section VI).

3. Validation Data

Appropriate validation data to support the analytical procedures should be submitted. Individual values as well as summary tables should be provided. Representative instrument output and raw data and information regarding stress studies should be included (see section VII).

686
687 *4. Results*
688
689 The results obtained by the applicant for the submitted samples should be provided.
690 Alternatively, COAs could be submitted. The dates of analysis should be stated.
691
692 *5. Composition*
693
694 The components and composition of the drug product should be provided.
695
696 *6. Specification*s
697
698 The specifications for the drug substance and the drug product should be included.
699
700 *7. Material Safety Data Sheets*
701
702 The applicant should include material safety data sheets (MSDSs) for all samples,
703 standards, and reagents (29 CFR 1910.1200(g)). As appropriate, MSDSs should be
704 provided for other materials used in the analytical procedures listed in the methods
705 validation package. In the case of toxic or hazardous materials, MSDSs should be
706 posted on the outside of the package to facilitate safe handling.
707
708 **B. Selection and Shipment of Samples**
709
710 On request from CDER, an NDA or ANDA applicant must submit samples of drug product,
711 drug substance, noncompendial reference standards, and blanks, so that the suitability of the
712 applicant=s drug substance and drug product analytical procedures can be evaluated by FDA
713 laboratories (21 CFR 314.50(e) and 314.94(a)(10)). For BLAs and PLAs, representative
714 samples of the product must be submitted, and summaries of the results of tests performed on
715 the lots represented by the submitted sample must be provided (21 CFR 601.2(a) and
716 601.2(c)(1)(vi)).
717
718 For CDER products, the number of sets of samples that should be submitted for methods
719 validation will be identified in the instructions forwarded to the applicant by the FDA
720 laboratory. In general, the quantity of samples in each set should be double the amount
721 needed to carry out the testing as performed by the applicant. Along with the drug substance
722 and the drug product samples, the applicant should submit internal standards, non-USP
723 reference standards, samples of impurities, degradation products, and unusual reagents. A set
724 of samples will be shipped to each assigned laboratory.
725
726 For biological products, CBER should be consulted on the submission of samples and
727 supporting materials.
728

Unless specified differently by the reviewer, samples from any batch, preferably samples from an aged batch, may be selected for NDAs and NDA supplemental applications. The submitted drug product samples should be from a batch made with the proposed market formulation. For ANDAs and appropriate supplements, a sample of the finished product from a batch being used to support approval of the submission should be used. If a sample is selected from a batch not described in the application, an amendment containing a copy of the batch record and certificate of analysis should be provided to the ANDA. For supplements that do not require submission and review of an exhibit batch record and associated data, any commercial batch may be submitted. For biological products, samples from several consecutively manufactured batches should be submitted.

The drug product should be supplied in its original packaging. Bulk substances (e.g., drug substances, impurities, excipients) should be stored in opaque nonreactive containers. To prevent breakage during shipping, the samples should be adequately packaged in a sturdy container. Samples shipped from outside the United States should contain the appropriate customs forms to reduce delay in delivery.

If special storage precautions (e.g., freezing, use of an inert gas blanket) are required to protect sample integrity, arrangements should be made in advance with the validating laboratory for scheduled direct delivery. If a sample is toxic or potentially hazardous, the container should be prominently labeled with an appropriate warning and precautionary handling instructions.

C. Responsibilities of the Various Parties

1. Applicant

In the sections of the application on analytical procedures and controls, the applicant should provide a name, address, telephone number, and facsimile number so that samples can be requested. If this information is not provided, the contact person and address listed in the NDA, ANDA, BLA, or PLA submission will be used.

The methods validation packages should be compiled and submitted with the NDA or ANDA submission. For BLAs and PLAs, a separate methods validation package need not be submitted.

When an FDA laboratory contacts the applicant for samples, the applicant should provide FDA laboratories with the samples within 10 working days. With the exception of sample delivery arrangements, all communications concerning validation at the FDA laboratories should be made through or with the knowledge of the review chemist for CDER applications, or the BLA/PLA committee chair for CBER applications.

2. Review Chemist

The review chemist will review the application to determine that the analytical procedures are adequate to ensure the identity, strength, quality, purity, and potency of the drug substance and/or drug product. Any changes in the methods resulting from the review of the application may require resubmission of the methods validation package. The review chemist, in coordination with the appropriate FDA laboratories, will decide which analytical procedures are to be validated. Comments from the FDA laboratories, if any, will be forwarded by the review chemist to the applicant on completion of the studies by the laboratories.

3. FDA Laboratory

An FDA laboratory will contact applicants with instructions on the submission of samples and the addresses to which samples should be mailed. The laboratory will test the samples according to the submitted analytical procedures to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes. Results and comments will be forwarded to the review chemist on completion of the studies.

4. Investigator

The investigator inspects the analytical laboratory testing sites where the release and stability testing are performed to ensure that the analytical procedures are performed in compliance with CGMP/GLP.

XI. METHODOLOGY

Sections II through IX provide general information on the submission of analytical procedures and methods validation information, including validation characteristics. Additional information on certain methodologies is provided below.

A. High-Pressure Liquid Chromatography (HPLC)

The widespread use of HPLC analytical procedures and the multitude of commercial sources of columns and packings frequently have created problems in assessing comparability. Many of the following points may also apply to other chromatographic analytical procedures.

1. Column

The following characteristics are useful for defining a particular column and, if known, should be included in the analytical procedure description. If method development has

indicated that columns from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one column is suitable, a listing of columns found to be equivalent should be included.

a. Column Parameters

- Material: glass, stainless steel, plastic
- Dimensions: length, inner diameter
- Frit size
- Filter type
- Precolumn and/or guard column type, if used

b. Packing Material

- Particle type: size, shape, pore diameter
- Surface modification (e.g., bonded surface type, surface coverage, percent carbon, additional silylation)
- Recommended pH range for column use

2. System Suitability Testing

Each analytical procedure submitted should include an appropriate number of system suitability tests defining the critical characteristics of that system. Criteria for all system suitability testing should be provided. The system suitability tests listed below are defined in CDER=s reviewer guidance on *Validation of Chromatographic Methods* (November 1994).

- Tailing factor
- Relative retention
- Resolution
- Relative standard deviation (RSD)
- Capacity factor
- Number of theoretical plates

The RSD is normally performed at the beginning of the run. However, for assays with lengthy run times or as otherwise justified by the applicant, the reported average may be taken from injections at the beginning and end of the run, or at the beginning, middle, and end of the run.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredients should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks

eluting closest to each other, should be given.

3. Operating Parameters

The sequence of injection of blanks, system suitability standards, other standards, and samples should be defined. Flow rates, temperatures, and gradients should be described.

Complete details should be provided for the preparation of the mobile phase, including the order of addition of the reagents and the methods of degassing and filtration. The effect of adjustments in mobile phase composition on retention times should be included in the analytical procedure. The rationale for the use of precolumns and/or guard columns should be provided and justified. Any special requirements, such as the use of inert tubing or injection valves, should be specified.

B. Gas Chromatography (GC)

At a minimum, the following parameters should be included in the description of a GC procedure. Additional parameters should be specified if required by the analytical procedure. If method development has indicated that columns from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one column is suitable, a listing of columns found to be equivalent should be included.

1. Column

- Column dimensions: length, internal diameter, external diameter
- Stationary phase
- Column material (e.g., silica, glass, stainless steel)
- Column conditioning procedure

2. Operating Parameters

- Gases: purity, flow rate, pressure
- Temperatures: column, injector, detector (including temperature program, if used)
- Injection (e.g., split, splitless, on-column)
- Detector
- Typical retention time and total run time

3. System Suitability Testing

Appropriate system suitability criteria should be defined and included in all analytical procedures.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredient should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks eluting closest to each other, should be given.

The RSD is normally performed at the beginning of the run. However, for assays with lengthy run times or as otherwise justified by the applicant, the reported average may be taken from injections at the beginning and end of the run, or beginning, middle, and end of the run.

C. Spectrophotometry, Spectroscopy, Spectrometry and Related Physical Methodologies

These analytical procedures include, but are not limited to, IR spectrophotometry, near IR spectrophotometry (NIR), UV/visible spectrophotometry (UV/Vis), atomic emission and atomic absorption, NMR, Raman spectroscopy, MS, and XRD.

Spectrometric analytical procedures may not be stability-indicating. The bias of the analytical procedure should be evaluated by comparing it with a chromatographic procedure, where appropriate. When manually operated equipment is used, the description of the analytical procedure should include an acceptance criterion for the amount of time that may elapse between sampling and reading. Appropriate system suitability and/or calibration testing is recommended. Validation criteria should include specificity (demonstrating no interference of placebo), linearity, repeatability, intermediate precision, and robustness.

D. Capillary Electrophoresis (CE)

At a minimum, the parameters listed below should be specified for a capillary electrophoretic analytical procedure. Additional parameters may be included as required by the procedure. If method development has indicated that capillaries from only one commercial source are suitable, this information should be included as part of the analytical procedure. If more than one capillary is suitable, a listing of capillaries found to be equivalent should be included.

1. Capillary

- Capillary dimensions: length, length to detector, internal diameter, external diameter
- Capillary material
- Capillary internal coating (if any)

2. Operating Parameters

- **!** Capillary preparation procedure: procedure to be followed before the first use, before the first run of the day, before each run (e.g., flush with 100 millimolar sodium hydroxide, flush with running buffer)
- **!** Running buffer: composition, including a detailed preparation procedure with the order of addition of the components
- **!** Injection: mode (e.g., electrokinetic, hydrodynamic), parameters (e.g., voltage, pressure, time)
- **!** Detector
- **!** Typical migration time and total run time
- **!** Model of CE equipment used
- **!** Voltage (if constant voltage)
- **!** Current (if constant current)
- **!** Polarity (e.g., polarity of electrode by detector)

3. System Suitability Testing

Each analytical procedure should include the appropriate system suitability tests defining the critical characteristics of that system. Other parameters may be included at the discretion of the applicant.

If an internal standard is used, the minimum acceptable resolution between the internal standard and one or more active ingredient should be specified. If the analytical procedure is used to control the level of impurities, the minimum resolution between the active ingredient and the closest eluting impurity, or the two peaks eluting closest to each other, should be given.

E. Optical Rotation

Optical rotation is used for the measurement of stereochemical purity. Visual polarimeters rely on a monochromatic source, which traditionally was sodium D, but has expanded to virtually any wavelength.

If measurements are to be made at a wavelength other than sodium D, an explanation for selecting the wavelength should be given, along with a comparison of the specific rotation at sodium D and the wavelength to be used. Circular dichroism (CD) spectra may suffice for this purpose. In addition to the provisions of USP <781>, procedures for measurement of specific rotation should include the solvent, concentration, and, for aqueous solutions, the pH to which the solution should be adjusted. The conditions and equipment should be shown to be suitable to confirm the stereochemical identity of a racemate or an enantiomer.

The enantiomeric purity can be expressed as *enantiomeric excess* (e.e.), using the following formula as an example:

e.e. = 100% * {{M} - [m]}/{[M] + [m]}

where [M] and [m] are the concentrations of the major and minor enantiomers, respectively. This yields values of zero for a racemate and 100 percent for a pure enantiomer. An intermediate concentration gives intermediate values; for example, 97:3 would give an e.e. of 94 percent.

Appropriate system suitability and/or calibration testing is recommended. Validation criteria should include specificity, and intermediate precision.

F. Methodologies Relating to Particle Size Analysis

Particle size analysis is an important element for quality control and regulatory evaluation of certain drug substances and drug products. The normal concepts of validation may differ for particle size methodologies as compared to other analytical methodologies such as HPLC. However, a standard mixture may be used for calibration.

Particle size evaluation can include characteristics of size, morphology, surface, and population of particles. The following parameters are useful for describing particle size analysis for characterization of drug substances and drug products.

1. Particle Size Methods

Types of particle size methods include, but are not limited to:

a. Nonfractionation methods that evaluate an entire population of particles

- Microscopy (optical, electron)
- Light scattering (dynamic, photon correlation, laser diffraction)
- Electrozone sensing
- Photozone sensing

b. Fractionation methods that use physical techniques to separate particles on the basis of size

- Sieving
- Cascade impactor
- Sedimentation
- Size exclusion chromatography

2. Calibration and Validation Characteristics

To ensure proper instrument operation, the system should be calibrated according to the manufacturer's and/or the laboratory's specification, as appropriate.

The methods validation usually involves evaluation of intermediate precision and robustness. Assurance should be provided that the data generated are reproducible and control the product's quality. See additional information in sections V and VII.

G. Dissolution

The equipment used for dissolution is covered by USP <711> or USP <724>. The dissolution procedure description and validation should include the following.

1. Dissolution Medium

A brief discussion of the reasons for selecting the medium.

2. Procedure

A dissolution test consists of a dissolution procedure and method of analysis (automated on-line analysis or manual sampling followed by HPLC analysis). The written procedure should cover the following items:

- Apparatus
- Preparation of standard
- Preparation of sample
- Method of analysis (e.g., UV, HPLC)
- Sampling procedure (e.g., intervals, filtration, handling of samples, dilutions)

- Calculations
- Acceptance criteria

Regardless of the method of analysis, system suitability criteria should be described. Blank and standard solution spectra or chromatograms should be included.

3. Validation Characteristics

Both the dissolution procedure and the method of analysis should be validated.

The time needed for the completion of the sample analysis should be stated in the procedure. Data should be submitted to support the stability of the dissolution sample during the procedure. If filters are used on-line or during sample preparation, appropriate recovery studies should be performed and documented and any bias should be addressed.

H. Other Instrumentation

1. Noncommercial Instrumentation

FDA encourages the development and use of the most appropriate instrumentation. However, the use of rare or exotic systems not only places an undue burden on the regulatory laboratory, but also may delay the validation process.

When noncommercial instrumentation is used, the instrumentation should be capable of being constructed from commercially available components at a reasonable cost, if possible. For unique methodologies or instrumentation requiring contract fabrication, the applicant's cooperation with the FDA laboratories in helping facilitate duplication of the analytical procedure is important. In addition to design and equipment specifications, complete performance assessment procedures should be provided. Such systems may be found suitable for regulatory use.

2. Automated Analytical Procedures

The use of automated analytical procedures, although desirable for control testing, may lead to delay in regulatory methods validation because FDA laboratories have to assemble and validate the system before running samples. To avoid this delay, applicants should demonstrate the equivalence of a manual procedure to the automated procedure based on the same principle whenever possible.

ATTACHMENT A
NDA, ANDA, BLA, AND PLA SUBMISSION CONTENTS

The information relating to analytical procedures and methods validation that should be submitted in NDAs, ANDAs, BLAs, and PLAs is identified below with a cross-reference to the section of this guidance that provides recommendations and/or discussion on the topics.

Information that should be included in the analytical procedures and controls sections

!	Reference standard information	Section IV
•	Analytical procedures	Section III, VI
•	Validation data	Section VII
•	Stress studies	Section VII.A.2.c
•	Instrument output/raw data for impurities	Section VII.A.2.b
•	Statistical analysis	Section VIII
•	Revalidation, as needed	Section IX

Information that should be included in the methods validation package[5]

•	Contents of the MV Package	Section XI
•	Representative instrument output/data for stress studies	Section VII.A.2.c
!	Representative instrument output and raw data for initial and oldest sample of a batch	Section VII.A.2.b

Information that should be included in the stability section

!	Stress study designs and results	Section VII.A.2.b
!	Reference (volume and page number of submission) to instrument output and raw data submitted to the section dedicated to analytical procedures and controls	Section VII.A 2.c

[5] For BLAs and PLAs, a separate methods validation package need not be submitted. Information similar to what is listed here should be included in the BLA or PLA submission.

ATTACHMENT B

METHODS VALIDATION PROBLEMS AND DELAY

Listed below are examples of common problems that can delay successful validation.

- Failure to provide a sample of a critical impurity, degradation product, internal standard, or novel reagent

- Failure to submit well-characterized reference standards for noncompendial drugs

- Failure to provide sufficient detail or use of unacceptable analytical procedures. For example:

  - Use of arbitrary arithmetic corrections
  - Failure to provide system suitability tests
  - Differing content uniformity and assay analytical procedures without showing equivalence factors for defining corrections as required by the current USP chapter <905> - Uniformity of Dosage Units

- Failure to submit complete or legible data. For example:

  - Failure to label instrument output to indicate sample identity
  - Failure to label the axes

- Inappropriate shipping procedures. For example:

  - Failure to properly label samples
  - Failure to package samples in accordance with product storage conditions
  - Inadequate shipping forms (e.g., missing customs form for samples from outside the United States)

- Failure to describe proper storage conditions on shipping containers

REFERENCES

FDA Documents[6]

Guidance for Industry: *ANDAs: Impurities in Drug Products* (Draft, December 1998).

Guidance for Industry: *ANDAs: Impurities in Drug Substances* (February 2000).

Guidance for Industry: *CMC Content and Format of INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products* (Draft, December 1997).

Guidance for Industry: *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (February 1995).

Guidance for Industry: *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production* (Draft, September 1998).

Guidance for Industry: *Stability Testing of Drug Substances and Drug Products* (Draft, June 1998).

Guidance for Industry: *Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances* (November 1994).

Guidance for Industry: *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).

Reviewer Guidance: *Validation of Chromatographic Methods* (November 1994).

FDA CDER MAPP 5221.1 *Requesting Methods Validation for ANDAs* (November 1998).

International Conference on Harmonization Guidances

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)

[6] Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form.

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)

ICH *Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (March 1999)

U.S. Pharmacopeia/National Formulary

Chapter <621> Chromatography; US Pharmacopeia 23, United States Pharmacopeial Convention, Inc., Rockville MD: 1994

Chapter <781> Optical Rotation, US Pharmacopea 23, United States Pharmacopeial Convention, Inc., Rockville, MD: 1994

Chapter <1225> Validation of Compendial Methods; US Pharmacopeia 23, United States Pharmacopeial Convention, Inc., Rockville MD: 1994

Interpretation and Treatment of Analytical Data; USP Pharmacopeial Forum, United States Pharmacopeial Convention, Inc., Rockville MD: 1994, Volume 24, Number 5, pp. 7051 - 7056

Other

Miller, J.C., J.N. Miller, and E. Horwood, *Statistics for Analytical Chemistry*, 3rd edition, Prentice Hall, 1993.

Saunders, B.D., and R.G. Trapp, *Basic and Clinical Biostatistics*, 2nd edition, Appleton and Lange, 1994.

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Active moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)). The active moiety is the entire molecule or ion, not the *active site*.

Detection Limit: The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated as an exact value.

Drug Product: A finished dosage form, for example, a tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug Substance/Active Ingredient: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body. The active ingredient does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

Placebo (or Blank): A dosage form that is identical to the drug product except that the drug substance is absent or replaced by an inert ingredient or a mixture of the drug product excipients quantitatively equivalent to those found in the drug product dosage form.

Quantitation Limit: The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

Reagent: For analytical procedures, any substance used in a reaction for the purpose of detecting, measuring, examining, or analyzing other substances.

Specification: The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of the drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials.

Spiking: The addition of a small known amount of a known compound to a standard, sample, or placebo, typically for the purpose of confirming the performance of an analytical procedure or the calibration of an instrument.

Stability-Indicating Assay: A validated quantitative analytical procedure that can detect the changes with time in the pertinent properties (e.g., active ingredient, preservative level) of the drug substance and drug product. A stability-indicating assay accurately measures the active ingredients without interference from degradation products, process impurities, excipients, or other potential impurities.

Working Standard: A standard that is qualified against and used instead of the reference standard (also known as *in-house* or *secondary standard*).