U.S. Food and Drug Administration
Center for Drug Evaluation and Research

GUIDELINE FOR SUBMITTING SAMPLES AND

ANALYTICAL DATA FOR METHODS VALIDATION

February 1987

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GUIDELINE FOR SUBMITTING SAMPLES AND ANALYTICAL DATA FOR METHODS VALIDATION

I. INTRODUCTION

This guideline is intended to assist applicants in submitting samples and analytical data to the Food and Drug Administration (FDA) for methods evaluation. The guideline is designed to expedite a portion of the review/approval procedure for New Drug Applications (NDA's) including Abbreviated New Drug Applications (ANDA's). It does not pertain to biological products, medical devices, or radiopharmaceutical drug products.

The guideline is issued under 21 CFR 10.90. An applicant (or sponsor) may rely upon the guideline in the presentation of data, assembly of information, and submission of materials to FDA concerning specifications and methodologies as required by 21 CFR 314.50, or may follow a different approach. When a different approach is chosen, a person is encouraged to discuss the matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

Some individual drug products may not require submission of all the information described in the guideline. In other cases, additional

detail may be needed to provide a rational, scientific foundation for proposed specifications and methodologies. Generally, however, the provisions of 21 CFR 211.194(a)(1) and (2) are descriptive of the kinds of information to be submitted.

Regulatory methods validation will normally be carried out by FDA after the NDA has been submitted. Under certain circumstances, however, such as in the case of new drugs potentially representing either important (Type A) or modest (Type B) therapeutic advances (defined in the Center for Drugs and Biologics Staff Manual CDB 4820.3), validation may be requested and performed during Phase III of the Investigational New Drug Application (IND). In such cases the same supporting information described in Section III of this Guideline should be submitted.

II. DEFINITIONS

A. Regulatory Specifications are the defined limits within which physical, chemical, biological, and microbiological test results for a drug substance or drug product should fall when determined by the regulatory methodology. For compendial articles, the specifications in the current edition of the United States Pharmacopeia or the National Formulary (USP/NF) are those legally recognized under Section 501(b) of the Federal Food, Drug, and Cosmetic Act (the act) and are used by the agency when determining compliance with the act.

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B. Regulatory Methodology is the procedure or set of procedures used by FDA to ascertain whether or not the drug substance or drug product in conformance with the approved regulatory specifications in the NDA. Generally, a regulatory assay will be stability indicating. For USP/NF articles, the analytical test methods in the compendial monograph are those legally recognized under Section 501(b) of the act and are used by the agency when determining compliance with the act. However, compendial methods may require validation to establish their suitability for specific drug products.

C. Regulatory Methods Validation is the process whereby submitted analytical procedures are first reviewed for adequacy and completeness and then are tested as deemed necessary in FDA laboratories. Depending in part on the quality of submitted data, validation may range from step-by-step repetition of an assay procedure to more elaborate studies that include assessment of accuracy, precision, sensitivity, and ruggedness of the method.

III TYPES OF MATERIAL TO BE SUBMITTED

A. Samples

Four identical sets of samples as described in 21 CFR

314.50(e) should be set aside for methods validation until the

FDA reviewing chemist has completed the preliminary review of

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the methods validation package. When the reviewing chemist is satisfied that adequate information has been submitted, and has determined that the methods should be validated, the chemist will telephone the applicant and give the names and addresses of the laboratories to which samples should be submitted. In most instances the applicant will be instructed to send sample sets to two different FDA laboratories. It is expected that samples will ordinarily be provided to FDA within 10 working days of a request. The two remaining sets should be retained by the applicant in the event of loss or a need for replication of testing.

To expedite validation, FDA may request internal standards or unusual reagents or equipment. Whenever feasible, these items should be commercially available. Samples of impurities, precursors, or degradation products should also be submitted if critical to the assessment of the methods.

If a sample is toxic or potentially hazardous, the container should be prominently labeled with an appropriate warning and with precautionary handling instructions. In addition, if material safety data sheets (29 CFR 1910.1200(g)) were

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prepared for the drug substance or drug product, it would be helpful if these were included with the sample to facilitate safe handling.

If special storage precautions (e.g., freezing, use of an inert gas blanket, etc.) are required to protect sample integrity, arrangements for scheduled direct delivery to the validating laboratory should be made through the reviewing chemist.

B. Contents of the Methods Validation Package

A. Methods Validation Package will usually include information copied from pertinent sections of the NDA, such as the statement of composition, the new drug substance and drug product specifications, certificates of analysis for each sample submitted, and the regulatory analytical methods, as described below. To aid the reviewing chemist these copies should retain the original pagination of the NDA sections from which they were copied. Four copies of the Methods Validation Package should be included with the initial submission: one copy with the archival copy and three with the chemistry, manufacturing, and controls section of the review copy.

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All communications concerning validation at FDA Laboratories should be made through the reviewing chemist. Laboratories should be contacted directly by the applicant only when specifically authorized by the reviewing chemist.

Detailed information relating to the Package should include the following:

1. A Tabular Listing of All Samples To Be Submitted

Listing should show lot number, identity (with chemical name and structure where required for clarity), package type and size, and quantity to the extent described in 21 CFR 314.50(e).

2. A Listing of All Proposed Regulatory Specifications

Cross-reference by NDA page number to the detailed description of the respective analytical methods employed.

3. Information Supporting the Integrity of the Reference Standard

In general, it is expected that the tests and methods used to characterize the reference standard will be different from, and more extensive than, those used to control the new drug substance. It is desirable that such methods not be comparative (i.e., dependent upon

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the availability of a previously designated reference standard of the same drug substance). If a working standard is used, it should be characterized to the extent required for the particular analysis by comparison with the reference standard.

USP/NF standards do not require further characterization. A noncompendial standard should be of the highest purity that can be obtained by reasonable effort, and it should be thoroughly characterized to assure its identity, strength, quality, and purity. Generally, this characterization includes the following:

a. If the synthesis of the reference standard differs from that of the new drug substance, a brief description of the synthesis should be submitted, along with any additional purification procedures used in its preparation regardless of the route of synthesis.

b. The information characterizing the reference standard, including legible reproductions of the relevant spectra, chromatograms, thin layer chromatography plates, and other instrumental recordings, should be submitted.

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(1) The methods and tests used should be described in detail if they differ from those given elsewhere in the Methods Validation Package.

(2) The information to be supplied may include the following:

(a) A physical description of the material, including its color and odor.

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

(c) Appropriate chemical attributes, such as structural formula, empirical formula, and molecular weight. Information to substantiate proof of structure should include appropriate analytical tests, such as elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, nuclear magnetic resonance, and mass spectra as

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well as applicable functional group analysis. The spectra should be interpreted in detail in support of the claimed structure.

(d) Data establishing purity. The data should be obtained by using appropriate tests, such as thin layer, gas, and/or high-performance liquid chromatography, phase solubility analysis, and appropriate thermometric procedures.

4. A Detailed Description of Each Method of Analysis

If alternative methods are submitted, the applicant should designate the preferred regulatory method and provide a rationale for the choice. Each regulatory method should be presented in sufficient detail that a competent analytical chemist can reproduce the necessary conditions to obtain acceptable results. A more detailed "cookbook" method may reduce the amount of time required for validation, particularly when the pitfalls of a specific technique have been eliminated by careful wording.

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The following are typically included in a description of a method of analysis:

a. A statement of the principle of the method.

b. A listing of necessary reagents (United States Pharmacopeia, Analytical Reagent, Chemically Pure, etc.) test solutions, and mixtures with directions for their preparation. Unstable reagents should be identified, and storage conditions and usable shelf life specified.

c. A listing of all required instrumentation (e.g., instrument type, detector, cell dimensions, sensitivity requirements, column type and dimensions, recorder, etc.).

d. A list of instrumental parameters used (e.g., full-scale absorbance, milliamp range, flow rate, temperatures, etc.).

e. A step-by-step procedure including equilibration, extraction, and/or centrifugation times, weights, volumes, and system suitability or start-up parameters where required. (See Appendix B) Unusual hazards should be identified.

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f. Representative calculations with a tabulation defining all symbols and numerical factors.

5. Information Supporting the Suitability of the

Methodology for the New Drug Substance

Generally, this should include the following:

a. A summary flow chart of the synthesis of the new drug substance and a list of known impurities/side reaction products. This may be submitted either directly or by authorized reference to the appropriate Drug Master file.

b. Control of polymorphs/isomers.

c. Data demonstrating suitable accuracy, precision, and linearity over the range of interest (ca 80% to 120% of theory). Data demonstrating specificity of the methods and determination limits for degradation products or impurities should be included. These degradation products or impurities should be adequately identified and characterized.

d. Legible reproductions of representative chromatographs and instrumental recordings.

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6. Information Supporting the Suitability of the

Methodology for the Dosage Form

Generally, this should include the following:

a. Data demonstrating suitable accuracy, precision, and linearity over the range of interest (ca 80% to 120% of the label claim). Data demonstrating specificity of the methods and determination limits for degradation products or impurities should be included. These degradation products or impurities should be adequately identified and characterized.

b. Data demonstrating recovery from the sample matrix where the nature of the product so indicates.

c. Data demonstrating that neither the fresh nor degraded placebo interferes with the proposed method.

d. Legible reproductions of representative chromatographs and instrumental recordings.

e. Data characterizing day-to-day, laboratory-to laboratory, analyst-to-analyst, and column-to

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column variability. These data may be included to provide a further indication of reproducibility and, in a limited sense, ruggedness.

f. A degradation schematic for the active ingredient in the dosage form, where possible (e.g., products of acid/base hydrolysis, temperature degradation, photolysis, and oxidation).

NOTE: In general, a stability-indicating method will be employed as the regulatory method. If the assay is not stability indicating, then a limit test for the degradation product(s) must be submitted.

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Appendix A

Examples of Common Problems That Can Delay Successful Validation

A. Failure to include a sample of a critical impurity, degradation product, or internal standard necessary to assess the adequacy of the method.

B. Failure to list complete specifications, or the selection of unsuitable specifications, such as the following:

1. Unsubstantiated or overly broad ranges (broader than investigational data can support).
2. Specifications that do not account for assay limitations.

C. Failure to provide sufficient detail, or unacceptable choice of procedures, reagents, or equipment, such as the following:

1. Use of placebo blanks.
2. Use of arbitrary arithmetic corrections.
3. Use of instrumentation not commercially available without a full description of components and their assembly.
4. Use of single-source chromatographic columns, equipment, or reagents without full specifications to permit duplication.
5. Use of specialized tools or equipment that is not commercially available for sample Preparation.
6. Use of an internal standard or other reagent that is not commercially available.
7. Failure to provide system suitability tests for chromatographic systems.
8. Differing content uniformity and assay procedures without showing equivalency factors for defining corrections as required by the USP XXI [905]).

D. Failure to submit complete or legible data.

1. Failure to label chromatograms and spectra as to sample identity.
2. Failure to label x-rays and y-axes as appropriate.

E. Failure to submit well-characterized reference standards.

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Appendix B

High-Performance Liquid Chromatographic (HPLC) Methods

The widespread use of HPLC methods and the multitude of commercial sources of columns and packings frequently have created problems in assessing comparability during regulatory method validation. It is recognized that many of the following points may apply equally well to other chromatographic procedures. The following characteristics have been found useful for defining a particular column:

A. Packing Material

1. Particle type: size, shape, pore diameter.
2. Surface modification: bonded surface type, surface coverage, percent carbon, additional silylation.
3. pH range.

B Column Type

1. Glass or stainless steel.
2. Dimensions: length, inner diameter.

C. System Suitability Tests (as defined in USP XXI 621 p. 1221)

1. Number of theoretical plates.
2. Tailing factor.
3. Relative retention.
4. Capacity factor.
5. Resolution.
6. Relative standard deviation.

In practice, each method submitted for validation must include an appropriate number of system unsuitability tests defining the necessary characteristics of that system. Other parameters may be included at the discretion of the applicant or the agency.

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If an internal standard is employed, the minimum acceptable resolution between the internal standard and one or more active components must be specified. The maximum allowable relative standard deviation should also be specified. If the method in question is used to central the level of impurities, the minimum resolution between the active component and the most difficult to resolve impurity must be given.

If an external standard method is employed, the maximum tailing factor and maximum relative standard deviation may suffice.

Where method development has indicated that only the columns from one commercial source are suitable, this information should be detailed as part of the method. If mare than one column is suitable, a listing of columns found to be "equivalent" may expedite validation.

The effect of adjustments in mobile phase composition on retention times should be included in the method. Any pre-columns or guard columns must be described. The rationale for their use should be logically explained and justified.

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Appendix C

Other Instrumentation

A Noncommercial Instrumentation

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

Where noncommercial instrumentation is used, the instrumentation should, if possible, be capable of being constructed from commercially available components at a reasonable cost. For unique methodologies or instrumentation requiring contract fabrication, the applicant's cooperation with the agency laboratories in helping facilitate duplication of the method is needed. In addition to complete design and specification details, complete performance assessment procedures should be provided. Access to the applicant's apparatus may be requested for initial and/or comparative testing.

B. Automated Methods

Use of unusual automated methods of analysis, although desirable for control testing, may lead to delay in regulatory methods validation because the FDA laboratories must assemble and validate the system before running samples. To avoid this delay, applicants may demonstrate the equivalency of the automated procedure to that of a manual regulatory method based upon the same chemistry.

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* U.S. G.P.0:1990-281-794:20818

June 17, 1996 http://www.fda.gov/cder/guidance/ameth.htm