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Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT OF THE CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF AN APPLICATION

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GUIDELINE FOR THE FORMAT AND CONTENT OF THE CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF AN APPLICATION

INTRODUCTION

This guideline is intended to assist drug firms in preparing the chemistry, manufacturing, and controls technical section of applications to market new drugs or antibiotics for human use. The technical section is to be included in both the archival copy and the review copy of an application. The guideline is issued under 21 CFR 10.90. An applicant may rely upon the guideline in preparing the chemistry, manufacturing, and controls technical section of the application 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.

The chemistry, manufacturing, and controls technical section of an application should fully describe the composition, manufacture, and specifications of the drug product and of the drug substance, including its physical and chemical characteristics and stability. Where applicable, some of this information may be provided by reference to one or more current Drug Master Files (DMF's) on file with this agency. An

environmental assessment (EA) of the manufacturing process and of the ultimate use of the drug should be included as required by 21 CFR Part 25.

Amendments, supplements, and annual reports submitted subsequent to the original application should, to the extent necessary to the evaluation of the submission, conform to the format and contain the information described in this guideline. Amendments, supplements, and annual reports should refer to the original application by page number, using the same section headings as in the original.

Requirements for the chemistry, manufacturing, and controls technical section of an application are set forth in 21 CFR 314.50(d)(1). This guideline provides an overview of the organization and contents of the technical section. For more detailed guidance concerning the contents of this section, refer to the guidelines for submitting documentation on (a) the manufacture of the drug substance, (b) stability of human drugs and biologics, (c) analytical data for methods validation, (d) packaging of human drugs and biologics, and (e) manufacture of and controls for drug products (References 1 through 5). A guideline for filing DMF's (Reference 6) and a comprehensive guideline on formatting, assembling, and submitting applications (Reference 7) are also available.

I. DRUG SUBSTANCE

A. Description, Including Physical and Chemical Characteristics and Stability

1. Names—Provide the chemical name(s) and, as appropriate and available, the established (generic) and proprietary (brand) names, synonyms, Chemical Abstracts Service (CAS) registry number, and code number.

2. Structural formula—Provide the chemical structure (including stereochemistry, when applicable), molecular formula, and molecular weight.

3. Physical and chemical characteristics—Describe physicochemical characteristics including, where applicable, such information as description, solid-state form, solubility profile, melting point, pH, specific rotation, and refractive index (Reference 1, II.A.1).

4. Elucidation of structure—Supply physical and chemical data collected to elucidate and confirm the chemical structure of the drug substance (Reference 1, II.A.2).

5. Stability—Describe fully the studies on the stability of the new drug substance and include the results. Reference to stability information from prior studies or from the literature

may be used, as appropriate, to meet some or all of these requirements. Also, include information showing the suitability of the stability-indicating analytical methods used (Reference 2, II.B).

B. Manufacturer(s)—Provide the name and address of each facility, besides the applicant, that participates in manufacturing the drug substance (e.g., performs the synthesis, isolation, purification, testing, packaging, or labeling). Describe the operation(s) that each will perform (Reference 1, II.C).

C. Method(s) of Manufacture and Packaging—Provide a full description of the materials and method(s) used in the synthesis, isolation, and purification of the drug substance. This description should include a list of starting materials, reagents, solvents, and auxiliary materials with specifications or a statement of the quality of each. The description should include a diagrammatic flow chart of the synthesis and a detailed description of each step. Any alternate methods or variations in the synthesis should be included with an explanation of the circumstances under which they would be used. If the drug substance is prepared by fermentation or by extraction from natural sources (plant or animal), provide a full description of the process (Reference 1, II.D).

1. Process controls—Provide a full description of the control checks performed at various stages of the manufacture, processing, and packaging of the drug substance. The description should include the specifications and tests for pivotal and key/critical intermediates with justification for their use (Reference 1, II.E).

2. Container-closure system—Provide appropriate information about the characteristics of, and the test methods used for, the container, closure, or other component parts to assure their suitability for shipment of the drug substance. (Reference 4, III.A.4.)

D. Specifications and Analytical Methods for the Drug Substance—Provide a full description of the acceptance specifications and test methods used to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of drug products made from the drug substance. The methods and standards of acceptance should be sufficiently detailed to permit duplication and validation by FDA laboratories. Adequate documentation should be submitted to support the accuracy, specificity, sensitivity, and precision of the methodology and the integrity of the reference standard (Reference 1, II.E and F).

A copy of this section should also be included in each of the four copies of the methods validation package (Section III of this guideline).

Where test methods and specifications are included in an official compendium or other public standard (e.g., test methods and specifications for antibiotics in 21 CFR Part 436), the standard used should be cited.

E. Solid-State Drug Substance Forms and Their Relationship to Bioavailability—Appropriate specifications for the drug substance should be submitted to assure the bioavailability of the drug product. Such different solid-state forms as polymorphs, solvates, and amorphous forms, as well as particle size, can greatly affect bioavailability. Therefore, these forms should be carefully controlled, if present (Reference 1, II.G).

II. DRUG PRODUCT

A. Components—A list of components should include all substances to be used in the manufacture of the dosage form whether or not they appear in the drug product (Reference 5, II.A).

B. Composition--Include a statement of the quantitative composition, giving the weight or measure for each substance used in the

manufacture of the dosage form. The batch formula to be used for the manufacture of the drug product should be provided (Reference 5, II.B).

C. Specifications and Analytical Methods for Inactive Components—Provide a full description of the acceptance specifications and test methods used to assure the identity, quality, and purity of each inactive ingredient (Reference 5, II.C).

NOTE: Copies of each of the sections described in paragraphs A, B, and C, above, should be included in the four copies of the methods validation package (Section III of this guideline).

D. Manufacturer(s)—Provide the name and address of each facility involved in manufacturing the drug product (e.g., the drug processing, packaging, labeling, or control operations). Describe the operation(s) that each will perform (Reference 5, II.D).

E. Method(s) of Manufacture and Packaging

1. Process controls—Submit a copy of the master/batch production and control records or a comparably detailed description of the production process. A schematic diagram of the production process is often helpful. A description of in-process

controls, including analytical tests and appropriate data to support the specifications, should also be included (Reference 5, II.E.1 and F).

Reprocessing operations that can be anticipated should be described in the initial new drug application (NDA). After the NDA has been approved, reprocessing due to unforeseeable deviations from specifications must be covered by a supplemental application (Reference 5, II.E.2).

2. Container-closure system—Provide full information about the characteristics of, and test methods used for, the container-closure or other component parts of the drug product package to assure their suitability for packaging the drug product. Stability data should be developed for each different type of container/closure proposed for marketing the drug product. Also include a description of the packaging operation and relevant in-process controls (References 2, II.C.1; 4, III; and 5, II.D and E).

F. Specifications and Analytical Methods for the Drug Product—Provide a full description of the specifications and analytical methods necessary to assure the identity, strength, quality, purity, homogeneity, and bioavailability throughout the shelf life of the drug product. The methods and standards of

acceptance, including the sampling plan and the accuracy and precision of the analytical methods, should be sufficiently detailed to permit duplication and verification by FDA laboratories. If submitting alternate methods, designate the preferred regulatory method and provide your rationale for the choice. Where test methods and specifications are established by an official compendium or other public standard, cite the standard used (Reference 5, II.F).

Copies of this information should be included in the four copies of the methods validation package (Section III of this guideline).

G. Stability—Provide a complete description of, and data derived from, studies of the stability of the drug product, including information showing the suitability of the analytical method(s) used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for the drug product as packaged in the container in which it is to be marketed. If the drug product is to be put into solution at the time of dispensing, stability data should be included for the solution prepared as directed on the label. State the expiration dating period proposed to be shown on the label (Reference 2, II.C).

III. METHODS VALIDATION PACKAGE

The regulations specify in 21 CFR 314.50(e)(2)(i) that three copies of the analytical methods and related descriptive information (the "methods validation package") shall be submitted in the archival copy of the application. However, in the interest of expediting the methods validation process, the applicant is requested instead to include one copy of the methods validation package in the archival copy and submit three additional copies with the chemistry, manufacturing, and controls section of the review copy. A statement that this option has been taken should then be included in the archival copy. The methods validation package should be made up of photocopies of information from various pertinent sections of the application and should retain the original pagination of the sections from which the photocopies are taken (Reference 3, III.B).

IV. ENVIRONMENTAL ASSESSMENT

Provide an environmental assessment in accordance with 21 CFR Part 25, analyzing the potential environmental impact of the manufacturing process and of the ultimate use of the drug product (Reference 8).

REFERENCES

(1) Guideline for Submitting Documentation for the Manufacture of Drug Substances.

(2) Guideline for Submitting Documentation for Stability of Human Drugs and Biologics.

(3) Guideline for Submitting Samples and Analytical Data for Methods Validation.

(4) Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics.

(5) Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products.

(6) Guidelines for Drug Master Files (November 1978).

(7) Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications.

(8) Federal Register, April 26, 1985 (50 FR 16636).

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