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

GUIDELINE FOR SUBMITTING DOCUMENTATION FOR THE MANUFACTURE OF AND CONTROLS FOR DRUG PRODUCTS

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I. INTRODUCTION

This guideline concerns the documentation of the manufacturing process used to produce dosage forms and the accompanying quality control system intended for raw materials, in-process materials, and the finished dosage form suitable for administration. It is one of a series of guidelines covering topics relevant to the manufacturing and controls portion of investigational new drug applications (IND's), new drug applications (NDA's), and abbreviated new drug applications (ANDA's). The guideline does not impose mandatory requirements [21 CFR 10.90(b)]. It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude expending time and effort in preparing a submission that FDA may later determine to be unacceptable.

The information and data discussed in this guideline relate to the identity, strength, quality, and purity of the dosage form and the procedures for assuring that all batches manufactured conform to the appropriate specifications. Information relating to the container, closure, stability, and labeling are discussed in separate guidelines.

Information included in a Drug Master File (DMF) to satisfy the documentation needed to evaluate any particular part of the manufacture and controls for a drug product is acceptable provided the reference is specific, current, and applicable to the drug product described in the application. However, the agency will consider the information in a DMF only if written authorization is granted with specific reference to pertinent sections, including dates of submissions of the DMF. For information on preparing DMF's, refer to the Guideline for Drug Master Files.

II. DRUG PRODUCT (NDA's and ANDA's)

The following information should be included in the application:

A. Components

Provide a list of components, including all substances and in-process materials used in producing a defined finished drug or placebo product. List all substances used in the manufacture of a drug product whether or not they appear in the finished product, and state the quality designation or grade for each material (e.g., Americian Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)). Identify each component by its established name, if any, or by complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparations or other mixtures are used as components, their identity should

include a complete statement of composition and other information that will properly describe and identify these materials. Justify proposed alternatives for any listed substances by demonstrating that the use of these alternatives does not significantly alter the stability and bioavailability of the drug product and the suitability of manufacturing controls.

B. Composition

1. Statement of Composition

A statement of the quantitative composition should specify, by unit dose, a definite weight or measure for each active drug substance and a definite weight, measure, or appropriate range for all other ingredients contained in the drug product.

2. Batch Formula

Provide a complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. Submit a separate batch formula for each formulation of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product.

C. Specifications and Analytical Methods for Inactive Components

Provide acceptance specifications and the corresponding analytical methods for all inactive components of the formulation, regardless of whether they remain in the finished product. Limits and methods (applicable to the finished dosage form) for components that are removed in the manufacturing process should be included. Limits and methods must be included for potentially toxic components.

D. Manufacturer

State the name, location and, where appropriate, building number of each facility having a part in the manufacture or controls of the drug product. This includes the following, as appropriate:

1. Manufacturer(s) of the bulk drug substance(s).
2. Manufacturer(s) of the drug product.
3. Contract packager(s) and/or labeler(s).
4. Contract laboratories performing quality control tests on raw materials, drug substance, or the finished drug product.
5. Suppliers of components used in the manufacture of the drug product.

E. Methods of Manufacturing and Packaging

1. Production Operations

To facilitate the evaluation of the production and control of the drug product, submit a copy of the proposed or actual master/batch production and control records or a comparably

detailed description of the production process for a representative batch. Describe the manufacturing and packaging process for a representative batch, including a description of each production step, actual operating conditions, equipment to be utilized and points of sampling for in-process controls.

A schematic diagram of the production process is often helpful. Such a diagram should include a superimposed materials flow plan, indicating the equipment used and the points of sampling.

2. Reprocessing Operations

Before reprocessing a drug product, the applicant should consider the effects of reprocessing on stability and bioavailability. To permit approval of the reprocessing of batches of bulk, in-process, and finished drug products that do not conform to established specifications, the original submission of an NDA may include proposals for reprocessing procedures that cover possible foreseeable deviations from specifications (e.g., weight variation, content uniformity, unacceptable tablet coating, etc.). Such reprocessing may require additional amounts of one or more of the components; however, the amounts added should not result in a component being present beyond the reasonable variations provided for in the formulation.

Reprocessing due to deviations not anticipated in the original NDA should be covered by a supplemental application. Approval of reprocessing procedures must be obtained before release of the reprocessed drug or drug product. These supplements may be directed to the reprocessing of a specific lot/batch or may be submitted as a new procedure. Supplemental applications for reprocessing should include the following:

a. A specific and complete description of the rejected material including a statement of the deviation(s) from the specification(s).

b. A detailed description of the proposed reprocessing procedure, including controls beyond those established for routine production.

c. A statement of the maximum time elapsed between the initial manufacture and the time of reprocessing, and the storage conditions during this interval.

F. Specifications and Analytical Methods for the Drug Product

1. Introduction

The goal of drug product manufacture is reproducibility within all specified limits. The significant chemical and physical parameters important to clinical response of the

drug product should be defined at an early stage in the investigational studies, so that the transition to routine production lot manufacture may be conducted rationally. A well-organized drug application should demonstrate that the manufacturing, sampling, and control processes have been designed to provide a consistent product that, within any lot and on a lot-to-lot basis, does not vary beyond the established specifications.

2. Sampling Methods

Describe the sampling plan that will be used to assure that the sample of the drug product obtained is representative of the batch. The plan should include both the sampling of production batches and the selection of sub-samples for analytical testing. This plan will, of course, be applicable only to batches of that particular size, so procedures for scale-up or scale-down of this sampling plan to other batch sizes must also be provided. If samples are pooled, a justification must be given for pooling them.

3. In-Process Controls

The analytical controls used during the various stages of manufacturing and processing of the dosage form should be fully described. Where feasible, the in-process specifications should be supported by appropriate data that

may include, but should not be limited to, representative master/batch production and control records. In particular, when these records are submitted in support of a supplemental application that proposes the deletion or broadening of specifications, the records should cover a consecutive series of batches. Information on in-process controls in manufacturing is essential to a thorough review of the manufacturing and processing of the drug.

4. Regulatory Specifications and Methods for Drug Products

Regulatory specifications are the defined limits (e.g., physical, chemical, biological, microbiological) within which test results for a drug substance or drug product should fall when determined by the regulatory methodology. The regulatory methodology is the procedure or set of procedures used by the FDA to ascertain whether or not the drug substance or drug product is in conformance with the approved regulatory specifications in the NDA. (See "Guideline for Submission of Samples and Analytical Data for Methods Validation.")

The regulatory tests and specifications should be designed to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf life of the marketed product. As such, regulatory

specifications normally include all criteria that apply to the bulk dosage form, those related to the packaged product, and those that indicate the presence or absence of degradation.

Regulatory specifications may differ from in-house product release specifications. All drug products require assay and identity tests and specifications. For compendial products, the specifications and tests in the United States Pharmacopeia/National Formulary (USP/NF) monographs may satisfy relevant requirements. Additional specifications or alternate analytical methods (e.g., tests for impurities, a stability-indicating assay, a second identity test, etc.) may be required as necessary. Broader limits than those in the USP/NF monograph will not ordinarily be approved as regulatory specifications unless the labeling indicates that the product differs from the official monograph. When alternate analytical methods that are equivalent to, or that are an improvement over, the compendial methods are submitted to the agency, the applicant is encouraged to simultaneously ask the United States Pharmacopeial Convention (USPC) to change or modify the methodology in the monograph.

Assay and identity specifications using a well-characterized reference standard and description of physical characteristics (e.g., appearance, odor, etc., where applicable) are required. A description of other attributes should also be considered for inclusion, depending on the type of dosage form. The following list is advisory, and is not exhaustive, and the omission of a parameter from the list should not lead to the conclusion that it cannot be the subject of a regulatory test under appropriate circumstances.

a. Tablets, capsules, and other solid dosage forms

(1) Uniformity of dosage units.

(2) Rate of release of the active ingredient from the dosage form by methodology (e.g., dissolution rate), as appropriate for the dosage form.

(3) Moisture content, where applicable. Special consideration should be given to dosage forms in which a major component is known to be hygroscopic.

(4) Softening or melting points for suppositories.

b. Solutions (including sterile solids for injection)

(1) Clarity, limit of particulate matter, assay of preservative, isotonicity (for injectable and ophthalmic products), and pH determination.

(2) Sterility of injectable and ophthalmic products.

(3) Apyrogenicity of injectable products.

(4) Leakage test for ampules, aerosols, pouch packets, strips, tubes, etc.

(5) Metering tests and specifications (if metered dosage) and container pressure for aerosols.

(6) Completeness and clarity of constituted solutions.

c. Suspensions

(1) Assay of preservative and pH determination.

(2) Sterility of injectable and ophthalmic products.

(3) Apyrogenicity of injectable products.

(4) Particle size specifications, resuspendability, viscosity, sedimentation rates, caking, and syringability of suspensions.

(5) Metering tests and specifications (if metered dosage) and container pressure for aerosols.

d. Creams, emulsions, and ointments

(1) Assay of preservative and pH determination.

(2) Sterility where required.

(3) Homogeneity.

(4) Uniformity of dosage units as appropriate.

e. Transdermal delivery systems

(1) In vitro release rates.

(2) Uniformity of dosage units.

f. Diluent solutions

Full acceptance specifications and analytical methods, including assays for preservatives, should be included for diluents with dry solids or for liquid concentrates.

g. Sterile plastic devices containing active drugs

(1) In vitro release rates, sterility, and limits for residual ethylene oxide and its decomposition products, as applicable, in addition to the identity of all plastic components.

(2) Additional physical tests such as frame memory, resiliency, tensile strength, and seal integrity of the immediate package.

h. Placebos

A suitable test demonstrating the absence of the drug substance in the placebo.

III. INVESTIGATIONAL FORMULATIONS (IND's)

The following information should be included in the application:

A. Components

Provide a list of components, including all substances and in-process materials used in producing a defined investigational

drug product or placebo product. List all substances used in the manufacture of a drug product whether or not they appear in the dosage form and state the quality designation or grade for each material (e.g., ACS, USP, NF).

Each component should be properly identified by its established name, if any, or by complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparations or other mixtures are used as components, their identity should include a complete statement of composition and other information that will properly describe and identify them. Justify proposed alternatives for any listed substances. An amendment should be filed for any significant changes in formulation not proposed in the initial IND.

B. Composition

Submit a quantitative statement of composition. It should specify an appropriate range or a definite weight or measure for each ingredient contained in the investigational drug product, whether active or not, and contain a batch formula representative of that to be used for the manufacture of the investigational drug product.

Each formulation of defined dosage forms, potencies/strengths, or significant changes of inactive ingredient(s) should be identified with a formulation number or other appropriate designation.

Include all ingredients in the batch formula regardless of whether they remain in the investigational drug product. The content of new drug substance indicated in the statements of composition and the representative batch formula should be on the basis of 100% potency/strengths as stated on the label. Any calculated excess of an ingredient over the label declaration should be designated as such, and percent excess should be shown. Explain any overage in the batch formula, other than that added to compensate for losses in manufacturing.

C. Specifications and Analytical Methods for Inactive Components

See section II. C. above.

D. Manufacturer

See section II. D. above.

E. Methods of Manufacturing and Packaging

A document describing proposed production and packaging operations should be submitted for IND phases. Although it would lack certain features of the final record, it should be as complete as possible under the circumstances.

F. Specifications and Analytical Methods for Investigational Drug Products

1. Introduction

The product tests and specifications appropriate to investigational drug products are, understandably, not as well developed as when an NDA is submitted. However, the safety of investigational products can be assured only if appropriate analytical information is provided. It is necessary to realize that the developmental studies of such methods are not so clearly separated into Phases 1, 2, and 3 as the clinical studies. The following is presented as a general IND development sequence intended to provide guidance for the development of product information during the investigational phases. The ultimate goal of this sequence is the development of the product tests and specifications in the form that will eventually be submitted with an NDA. The level of detail for specifications and analytical methods set forth in section II.F of this guideline must, therefore, be considered as an ultimate goal. The fact that an item may not be included in this section of this guideline should not be viewed as justification for its omission at a later development stage of the IND.

2. Phases 1 and 2

An assay method including adequate acceptance specifications for content of the new drug substance (including antibiotic) in the dosage form should be submitted. The initial limits need not be overly narrow but should be appropriately tightened as experience with the drug accumulates. Because the assay alone might not serve as a satisfactory identity test, using a different method may be necessary during these phases. Chemical and physical tests characterizing the dosage form that should be included for solid oral dosage forms are uniformity of dosage unit and dissolution profile in an appropriate medium. Sterility tests, a measure of particulate content, and apyrogenicity testing should be included for injectables.

The assay or other procedure should make use of a reference standard or interim standard, and analytical data to support its integrity should be submitted. (See "Guideline for Submitting Documentation for Manufacture of Drug Substances.")

Information should also be submitted to support the specificity, linearity, precision, and accuracy applicable to specific quantitative methods used to test the dosage form.

3. Phase 3

Provide a full description of the identity tests, assay methods, and acceptance specifications as well as any other appropriate chemical and physical characteristics of the dosage form. These should approach NDA requirements in the level of detail provided, including the suitability of specifications, and data to confirm the adequacy of the analytical methodology. In vitro dissolution rate tests and specifications should be submitted for solid dosage forms. Information in support of any reference standard should be comparable to that expected in an NDA submission.

4. Placebos

For matching placebos used in clinical studies, a full description should be provided of the precautions that will be taken to ensure the absence of the new drug substance from the placebo preparation. The placebo and active dosage form should be as similar as possible in physical characteristics and identical in packaging.