

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

**GUIDELINE FOR SUBMITTING SUPPORTING
DOCUMENTATION IN DRUG APPLICATION
FOR THE MANUFACTURE OF DRUG SUBSTANCES**

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I. INTRODUCTION

This guideline is intended to provide sponsors/applicants with procedures acceptable to the agency for complying with regulations pertaining to the submission of adequate information on the production and control of new drug substances. This guideline addresses new drug substances manufactured by chemical synthesis, by fermentation, or by isolation from natural sources (and combinations thereof); it does not cover drug substances manufactured by recombinant DNA synthesis (biotechnology methods). 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 spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

The need to provide adequate information related to drug manufacturing is imposed in section 505(b) of the Food, Drug, and Cosmetic Act, which requires a full description of the "methods used in the manufacture of such drug." Such a description includes the method of preparation of the drug substance, and the control testing used to monitor its identity, strength, quality, and purity.

A description of the methods of preparation and process controls is pertinent not only to a new drug application (NDA), but also to an abbreviated new drug application (ANDA), an investigational new drug application (IND), and appropriate portions of a drug master file (DMF).

For a new drug substance, a description of the "source and preparation" is a requirement in the IND stage of study under 21 CFR Part 312. Subsequently, when an IND is submitted, a description of the "methods used in the synthesis" are required under 21 CFR 314.50(d)(1)(i).

Production of a drug substance, whether by synthesis, fermentation, or isolation, usually starts with relatively impure or commercial grade (i.e., not of drug quality) materials. Subsequent steps of the procedure involve preparation and transformation of intermediates (with appropriate characterization and purification) to afford finally the new drug substance. The quality and purity of the drug substance cannot be assured solely by end-of-the-line testing, but depends on proper control of the manufacturing and synthetic process as well. Proper control and attainment of minimal levels of impurities thus require the following: (a) appropriate quality and purity of the starting materials, reactants, and reagents; (b) establishment and use of in-process controls for intermediates; (c) consistent adherence to validated process procedures; (d) adequacy of the final (release) control testing of the new drug substance. In addition to details of the manufacturing process and the in-process controls, information is also needed concerning the final stages of purification (or recrystallization) of the drug substance. Properties of the bulk new drug substance, such as solubility, solid-state forms, particle size and surface area, may be critical for the subsequent bioavailability and stability requirements of the final dosage form.

II. REQUIREMENTS FOR A NEW DRUG APPLICATION

A. Physical and Chemical Characteristics

1. Properties

The regulations require a full description of the physical and chemical characteristics of the drug substance. This requirement may be satisfied by the submission of information such as the following: name (generic name, chemical name, code number); Chemical Abstracts Service (CAS) number if available; description (e.g., appearance, color, physical state); molecular formula and molecular weight; structural formula (including ionic state if applicable); stereochemistry (identifying chiral centers, cis-trans isomerism, etc.); enantiomer or solid-state form ratios (e.g., for racemates, and for defined admixtures of isomers or enantiomers or solid-state forms); solubility profile (aqueous and nonaqueous as applicable); partition coefficients; solution pH; dissociation constant(s); melting or boiling point; refractive index; specific gravity. For drug substances that are proteins, see the "CRC Handbook of Biochemistry and Molecular Biology," "Methods in Enzymology," and related monographs for how protein properties may be described.

The items above are not necessary or appropriate for all submissions. Additional information may be required, particularly as the state of the art progresses.

2. Structure

The elucidation of structure (e.g., the data and its interpretation) should be based on appropriate physical and chemical test results. These may include the following: elemental analysis; mass spectrometry (MS); nuclear magnetic resonance (NMR), ultraviolet (UV), and infrared (IR) spectroscopy; molecular weight determination; stereochemistry and configurational or conformational analysis (e.g., optical and geometric isomers); X-ray analysis; degradative analysis (e.g., amino acid sequencing and/or analysis); chromatographic profile; other tests (e.g., functional group analysis, derivatization, complex formation).

Again, not all items are necessary or appropriate in all cases, and the listing should not be considered limiting (i.e., more analysis may be required as the state of the art progresses and the nature of the new drug substance demands). The actual data and the details of its interpretation should be placed in the section for Reference Standard (see II.F.2, and 3.).

B. Stability

The regulations require a full description of the stability of the drug substance. See the "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" for assistance in fulfilling this requirement.

C. Name and Address of the Manufacturer

The regulations require the application to contain the name and address of the manufacturer. Each site should be properly identified by street address, city, and State, and where appropriate the building number. If more than one building is involved, the submission should state which part of the operation is conducted in each building.

D. Manufacture of the Drug Substance

There are two principal reasons for requesting a detailed presentation of the synthetic pathway and/or manufacturing process. First, a particular synthetic pathway will typically be uniquely associated with a set of impurities (actual and potential), and also a specific solid-state form. The impurities may have significant clinical or toxicological effects. It should be noted that (even in racemates) enantiomers may be considered as impurities. Proper control of the synthetic process monitors impurity levels during the process and in the final bulk drug substance. When a change is made or proposed in a synthetic process, a different ratio or even different set of impurities may arise, and the control testing may need modification. The "United States Pharmacopeia" (USP) also states that tests, besides those provided in drug substance monographs, may be necessary when a change in the source of material or processing occurs.

Second, knowledge of the synthetic pathway provides additional evidence to support the proposed chemical structure. How the final drug substance molecule is assembled from the starting materials and reactants, and descriptions of the transformations performed in the steps of the synthesis, support the analytical information elucidating the structure. For example, the final stereochemical configuration may be related to that of the starting material, or may have been introduced by a stereospecific reaction or by resolution of an intermediate in the synthesis. Knowledge of the synthetic pathway would reveal which possibility is correct.

1. Material Controls

a. Starting material

(1) Definition of starting material

What constitutes the "starting material" may not always be obvious. For example, if a manufacturer carries out a simple final procedure, e.g., the esterification of a carboxylic acid, to yield the drug substance, he may consider the acid as the starting material. However, the full synthesis of this acid may well be, and frequently is, quite lengthy and/or difficult; the acid is thus not the actual starting material. Without reporting the full synthesis of this acid from the actual starting material(s), the manufacturer has not adequately described the synthetic process for evaluation by FDA. The complete synthesis from the actual starting materials should be submitted.

While a definition of starting material applicable to all situations cannot be given, the following criteria for defining a starting material may be helpful

- (a) It is incorporated into the new drug substance as an important structural element.
- (b) It is commercially available.
- (c) It is a compound whose name, chemical structure, chemical and physical characteristics and properties, and impurity profile are well defined in the chemical literature- (see Glossary).
- (d) It is obtained by commonly known procedures (this applies principally to starting materials extracted from plants and animals, and to semisynthetic antibiotics).

Frequently, the starting material will meet several of these criteria. If it does not meet any, it is probably not the starting material. When an applicant wishes to use a starting material that is not commercially available, the material should meet criterion (c). In addition, for material that is not commercially available, it may be necessary to carry out more testing for impurities than would be needed for a commercially available product.

The starting material may be the subject of a DMF (e.g., some starting materials for semisynthetic antibiotics). When the starting material is itself a drug substance, the synthesis of this material should be provided either in full or by authorized reference to an NDA or DMF. Generally the decision about what is the starting material has been reached by agreement between the applicant and the FDA chemist before submission of the NDA (e.g., during an IND End-of Phase 2 meeting, or pre-NDA meeting).

(2) Control procedures for starting materials

Starting materials should be listed. Acceptance specifications and tests defining identity, quality, and purity should be provided. The analytical test methods should be briefly described. The source of the starting material need not be identified, but may be requested.

A specific identity test should be performed, as well as an assay, with limits for impurities. In those cases where impurities (e.g., positional isomers of aromatic compounds) could be carried through to the drug substance, a purity profile should be provided (e.g., chromatography with quantitation/identification of impurities). Assurances or statements of quality from the supplier are acceptable for the profile, provided that the manufacturer establishes the reliability of the supplier's analyses through validation, initially and at appropriate intervals. These statements from suppliers should include specifications and results and should indicate the type of method used for analyses.

b. Reagents, solvents, and auxiliary materials controls

These chemicals should also be listed. The specifications and test methods for each such material should be stated, and/or a statement of quality provided. The applicant should describe the specific identity test performed (unless omitting such a test has been otherwise justified, e.g., because of hazard). The extent of additional testing performed -- whether by the supplier or by the applicant -- should be based on the role of the chemical in the synthesis. For example: a base (e.g., sodium hydroxide) used to neutralize excess acid in a synthetic reaction mixture would not normally require extensive purity testing; in contrast, an optically active organic acid used in a resolution step (e.g., one enantiomer of dibenzoyltartaric acid) would require such additional testing.

2. Synthetic Drug Substance

An applicant should provide complete information on the synthesis, from starting materials) to the bulk new drug substance. The description should contain a diagrammatic flow chart of the whole synthesis and a written statement for each step of the synthesis.

a. Flow chart of the synthesis.

The flow chart typically should contain the following:

- (1) Chemical structures of reactants (i.e., starting materials and intermediates, and also molecules incorporated into the structure) and products;
- (2) Stereochemical configurations, where applicable;
- (3) Intermediates (either in situ or isolated);
- (4) Solvents, catalysts, and reagents;

A ratio or mixture of products (e.g., two or more isomers) produced by a reaction should be shown in the flow chart. Significant side products and impurities, particularly those that interfere with the analytical procedures or are toxic, should be illustrated separately (see sections II.D.2.c, and II.F.3.).

b. Description of the synthesis

The written statement for each step of the synthesis, with greater detail included toward the final steps of the process, should include the following:

- (1) Typical equipment used for the reaction;
- (2) Reactants (starting material or intermediate used in the step, with chemical names and amounts);
- (3) Solvents, catalysts, and reagents (chemical names and amounts);
- (4) Conditions (temperature, pH, time, pressure, etc.);
- (5) Tests for completion of reaction, if employed;
- (6) Workup and isolation procedures;
- (7) Purification procedures for drug substance and for intermediates, if employed;
- (8) Yield ranges (crude and/or purified; weight and percent).

The final step of the synthesis and the isolation of the crude new drug substance, as well as its purification, should be provided in full detail. (See section II.D.2.c below regarding purification of the drug substance.)

Besides providing a written description of the synthesis which includes verified ranges for the operating parameters (refer to section II-E [Process Controls] and section IV [CGMP]) and for the expected yield, the applicant should provide a written example of actual practice, clearly identified as an example for the reviewer's information. This example should not be merely a copy of batch records but should contain more detail.

Any alternate method or permissible variation that may be employed (e.g., alternate starting materials, reactants, solvents, conditions, catalysts, isolation, and/or purification procedures)

should be reported. Comparative analytical data for the material produced by each variant synthetic method should be provided.

c. Purification of the drug substance

The description of the purification of the crude new drug substance and its isolation from the final reaction step mixture should be given in detail, and should include:

- (1) The yield ranges of the crude product;
- (2) Any tests performed on the crude product to determine its purity (see item 6, below);
- (3) A detailed description of the isolation and purification procedures (e.g., for recrystallization: the solvent used, the quantity of solvent in relation to the amount of crude product, whether it is filtered while hot, whether a decolorizing agent is used, the rate of cooling and the final temperature, the use or re-use of any mother liquors, and if second crops are obtained);
- (4) Alternative purification procedures (see the last paragraph of section II.D.2.b.; see also section II.G.);
- (5) The yield range (weight and percent) of the purified product;
- (6) Evidence demonstrating that the purification procedure improves the purity, such as before--and-after chromatographic illustrations.

This testing and information may be necessary only on initial production batches, if the purification process has been verified or validated.

d. Changes in the synthesis

Proposed changes in the synthesis should be submitted to the application as a supplement for an approved NDA or as an amendment to an IND, a DMF or a pending NDA. An approved supplement is required [21 CFR 314.70(b)(1)(iv)] to change the method of synthesis approved in the MIA for the drug substance, including a change in solvents.

When the route of synthesis is changed (i.e., reactions and/or intermediates are different from those approved in the NDA), comparative analytical data (i.e., a complete purity profile) for the drug substance made by each route should be provided. A special case, where the proposed change is to redefine the starting material; is discussed below.

When there is a change in the solvent used for the final crystallization of the new drug substance, the new drug substance should be examined for changes in crystalline form and/or solvation; refer to section II.G. The new drug substance must meet its original specifications for crystalline form and/or solvation.

Solvent changes for other reaction steps or purifications also require a supplemental application. The application should contain evidence that the change affords material

(compound or intermediate) of equivalent quality and purity, but morphology need not be considered.

An approved supplement is required (21 CFR 314.70(b)(1)) if an applicant wants to shorten the synthesis approved in the NDA or develop a new synthetic method by redefining the starting material, in order to employ a compound later in the synthesis that has become commercially available. This compound must have been an intermediate in the approved LEA synthesis, and must meet both the "b" and "c" criteria for starting material. The compound should be used at least two full steps before the new drug substance if possible (i.e., it should be prior to the final intermediate). Additional information on the characterization and purity profile of the starting material may be needed, depending on the adequacy of the literature references cited (copies should be provided). For compounds cited in journal articles, an elaboration of the published material (i.e., additional information about testing for impurities) may suffice. For compounds described in patents, both complete characterization and a full purity profile will usually be needed. Analytical test procedures used to qualify each new source/supplier of the new starting material should be described. A general testing protocol may be suitable.

The applicant should demonstrate by direct comparison (i.e., both by analyses and by a use test) that the compound is equivalent to the material used to make the new drug substance employed in the clinical trials, and that the acceptance tests and specifications for the compound are adequate. The use test should be at least on a pilot scale (i.e., larger than bench scale).

A commitment to submit results from thorough examination of the first three full-scale batches made with the material should be provided. The examination should be similar in scope and extent to the testing involved in qualifying a new reference standard.

For changes of the type permitted by 21 CFR 314.70(c)(3), an adequate synthesis description on file would facilitate a conclusion that changes in site of manufacture of the new drug substance do not require prior FAA approval for implementation.

3. Reference Standard

The original application should include a full description of the preparation of any reference standard substance used, including the description of the purification steps. See also section II.F.3.

4. In Situ Products (not isolated)

An in situ product is formed when the synthesis of the drug substance and the manufacture of the final product are carried out in the same operation, usually in solution. Examples are: lithium citrate syrup prepared from the in situ reaction of lithium hydroxide and citric acid, and lidocaine hydrochloride prepared in situ from a solution of lidocaine base and hydrochloric acid.

The description of the manufacture of an in situ product should be treated as for any other synthetic step (i.e., full descriptions of how the materials employed are prepared should be

given). While purification procedures and yield range information are not needed, successful formation of the desired product should be demonstrated.

5. Microencapsulation

Microencapsulation is a process in which small, discrete solid materials, liquid droplets, or gases are completely enveloped by an intact membrane. The functions of the capsular membrane are to protect the enclosed material and/or to control the flow of materials, inside and outside, across the membrane. The membrane may consist of an inert polymeric material (e.g., ethyl cellulose, gelatin, polyvinyl alcohol, etc.). Depending on the desired characteristics, a wide range of film thicknesses may be employed. A microcapsule may be free, consisting of a single particle, or it may be in the form of clusters of particles.

The manufacture of a microencapsulated drug substance is considered an extension of the synthesis or manufacturing process for the drug substance itself. Consequently, the same complete description should be submitted as for any other step. In addition, any special treatment or precautions involved in preparation and handling of the microencapsulated drug substance should be described.

6. Antibiotics and Other Drug Substances from Fermentation or Natural Sources

a. Fermentation

(1) Control procedures for starting materials

Fermentation processes use well-characterized microorganisms to convert by biosynthetic reactions, various sources of carbon, nitrogen, oxygen, etc., into antibiotics or other desired chemical substances. Biosynthetic control mechanisms, such as catabolite repression and substrate induction, which can affect yields and products mixes, may depend on the type of raw material used. An evaluation of a fermentation process thus begins with consideration of the starting materials. Starting materials (and any alternatives) should be listed and their specifications and (where applicable) degree of purity provided, with a brief description of the test methods. Special attention should be given to specifications for organic materials used in fermentations (e.g., starch, glucose, lactose, corn steep liquor, soy bean meal). Inorganic components used in fermentations should meet the same requirements as for chemical syntheses. When precursors or inducers are used, their specifications and tests should be provided.

(2) Microbial identification, source, deposition

The most critical factor in any fermentation process is the specific microorganism cultured. Therefore, proper strain identification should be performed according to known methods (e.g., "Bergey's Manual of Determinative Bacteriology"). The description of microbial identification should include morphological, cultural, and biochemical characteristics (e.g., cell shapes, size, appearance on the agar medium, utilization of various

carbon and nitrogen sources, temperature for optimal growth, aerobic or anaerobic conditions).

The source of the original microbial isolate (soil, water, air, etc.) should be described, and strain improvement procedures (e.g., notation or genetic engineering techniques) should be briefly described. If any microbial isolate of the producing organism has been sent to official culture collection organizations, the organization (e.g., American Type Culture Collection (ATCC); United States Department of Agriculture, Northern Regional Research Laboratory (NRRL) and its identification number should be provided in the application.

(3) Fermentation process monitoring and control

Antibiotic production in large-volume fermenters, and other microbial transformations, can be divided into three successive stages: (a) media preparation and sterilization; (b) fermenter inoculation; and (c), fermentation itself. Each step should be briefly described or characterized.

The description of media preparation should include: detailed media composition (i.e., the starting materials, precursors, etc. used); the method of media sterilization (e.g., directly in the fermenter or through a continuous sterilization system); the temperature and duration of sterilization; and the pH of the medium after sterilization.

A brief description of the fermenter inoculation should be included.

The description of the fermentation stage should include those parameters which are routinely monitored for the control of that fermentation: e.g., duration, temperature, pH, aeration rate (volume of air per volume of medium), concentration of dissolved oxygen, amount of reducing sugar, ammonium concentration. The critical, in-process controls should be indicated. If an antifoaming agent is used, its identity and concentration should be provided.

b. Extraction, isolation, analysis, characterization

At the end of the fermentation the amount of antibiotic or other drug substance present in the fermentation broth should be determined; the analytical procedure used should be described (see below). The description of the isolation and purification procedure should include both a diagrammatic flow chart and a written statement.

The flow chart should include the solvents (and/or reagents) used for each step and should give the purity (percent) of the product after each step. Conditions (e.g., temperature, pH) maybe included.

The written statement should include the following information for each step, where applicable:

- (1) Method of isolation and purification;
- (2) Procedure for precipitation (e.g., isoelectric, salting out, solvent addition);
- (3) Equipment;
- (4) Solvents and reagents;
- (5) Conditions (temperatures, pH, time);
- (6) Yields.

Analytical techniques) should be adequate for identification and quantitation of side products and impurities in the final bulk preparation, as well as for following the progress of purification. Once it has been shown that the isolation and purification procedure does (largely, and successively) remove side products and impurities, less sophisticated (i.e., less discriminating) methods may be used to routinely monitor the progress of isolation and purification.

The purified fermentation product should be completely characterized and (if possible) its structure determined. The characterization informatics should be comparable in extent and detail to that for a totally synthetic drug substance and should also include examination for solid-state forms (see sections II.F. and G.). Those specific analytical techniques which differentiate the product from related antibiotics should be described.

Minor active components of an antibiotic mixture should be identified and individually quantitated. In the case of an antibiotic preparation with several major active components, limits for each of these should be proposed based on their pharmacological and toxicological properties. Side products and impurities should be examined for toxicological properties, using either the final bulk preparation (containing the side products and impurities at the proposed limits) or the individually isolated material(s). (See Section II.F.2.d)

c. Drug substances obtained from plants and animals

(1) Plants

The description of the collection and preparation should include the botanical species and the part of the plant. Other factors which influence the quality or composition of the final product should be described. These factors may include the following:

- (a) Geographical location where the plant is grown;
- (b) Storage and transportation renditions;
- (c) Drying conditions;
- (d) Grinding conditions.

The description of the collection and preparation procedure should include the test methods) for identity and assay for the drug substance in the original and crude material(s). Typical results should be provided. The description of the

extraction and isolation procedures should include the same information, where applicable, as for antibiotics or fermentation products (section II.6.b.), with similar attention devoted to identification of impurities and minor components, and to the characterization of the material (including elucidation of structure).

(2) *Animals*

The description of the collection and preparation procedure should, where applicable, include:

- (a) Species, and organ or tissue used;
- (b) Statement(s) demonstrating compliance with USDA or equivalent requirements or regulations;
- (c) Conditions for storage and transport of the organ or tissue to the processing facility;
- (d) Drying conditions;
- (e) Grinding procedure.

The description should include the test methods) for identity and assay for the drug substance in crude materials(s), and typical results should be provided. The extraction and isolation procedure descriptions should include, where applicable, the same information as requested for antibiotics or fermentation products (section II.6.b.), and similar attention should be given to identification of impurities and minor components, and to characterization of the material (including elucidation of structure).

d. Semisynthetic antibiotics and other drug substances derived from fermentation and natural sources

The starting material for a semisynthetic antibiotic, or other drug substance derived from natural sources, is obtained by fermentation and/or extraction. The description of the starting material manufacture should be provided as indicated previously (section II.D.6.a, b, c) or by reference to a Due' as indicated in section II.D.1.a. The information for the synthesis of the final drug substance from this starting material should be provided as described in section II.D.2.

Precautions, including animal safety testing when appropriate, to detect, identify, and eliminate impurities (present in the naturally derived starting material or formed in subsequent chemical transformations) from the final product should be described.

Some of the transformations may be enzymatically catalyzed. In such cases the following information should be provided:

- (1) Biological source of the enzyme;
- (2) descriptive technical name of the enzyme;
- (3) descriptive information on the enzyme preparation, akin to that requested for chemical reagents (see section II.D.2.b.).

E. Process Controls

1. Intermediates and In-process Controls

The regulations require that controls (specifications and tests) be employed at selected intermediate stages of the synthetic process to assure that the synthetic and purification procedures are operating properly and that the intermediate tested is suitable for subsequent processing. The choice of which intermediate(s) or steps in the process to test, and the kind of testing required, are the responsibility of the applicant based on his experience during the development and verification of the total synthetic process. In early development work, every step would usually have been examined (at least for extent of reaction) and every intermediate at least partially characterized with some estimate of purity. As experience is gained with the synthesis, the critical reaction steps and intermediates to be monitored are selected. At the time of NDA submission, in-process control points should have been selected and appropriate specifications and tests established to meet the requirements of the regulations. This whole operation is part of the process validation of the synthesis.

The basis for selecting control points and intermediates should be explained, and the adequacy of the specifications and tests to control the synthetic process demonstrated. The ranges for the operating parameters in the written description of the synthesis should be chosen in light of the controls (specifications and tests). Generally, broad operating ranges will require stricter controls. (See also section II.E.b. (recovery and rework) below.) With additional experience subsequent to IAA approval, the choice and nature of in-process control procedures may require modification. Changes in in-process control procedures will require additional validation (see section IV).

Controls may be designed to (a) demonstrate that the desired product has been obtained; (b) determine a key physical property (e.g., melting point, optical rotation, etc.); (c) determine purity/impurity of the intermediate; (d) determine that the yield is within the normal operating range. In some cases no controls for the intermediate may be feasible (e.g., where they are held in solution, or are directly processed to the next compound). When appropriate, testing may consist only of a test designed to monitor the progress of the synthesis (i.e., reaction completion).

Same or all of the above kinds of process controls should be met at each point selected for in-process control testing. Pivotal, key, and final intermediates (see Glossary, and below) would ordinarily require at least the in-process controls listed above. To eliminate the need for heroic final cleanups, it is expected that the degree of purity of intermediates will increase progressively, from the first intermediate on to the drug substance itself.

a. Pivotal intermediates) (See Glossary.)

Any pivotal intermediate should be described in adequate detail (i.e., be well characterized) and be subject to rigorous examination procedures as part of the specifications and tests, including thorough chromatographic examination so as to avoid overlooking impurities arising from alternative syntheses. Such rigorous examination need not be routine but may be needed in special circumstances such as when the supplier or synthesis is changed. The degree of testing and the level of

purity required for a pivotal intermediate should increase as its position in the synthesis scheme approaches the final intermediate.

b. Key intermediates (See Glossary.)

The specifications should be adequate to assure that the molecular architecture necessary for the final product, as well as the requisite degree of purity, have been attained. Test procedures should thus show that the desired transformation (such as introduction of chirality, or a stereospecific reaction) has occurred in the manner expected and within the normal yield range expected, and show by quantitative determinations) that undesired materials (e.g., isomers, by-products, starting materials) are within established limits.

c. Final intermediate (see Glossary.)

Specifications and tests for final intermediate should be nearly as extensive and stringent as those for the new drug substance itself, because this is the last opportunity to monitor purity and impurities before the final reaction.

2. Reprocessing

Intermediates which do not meet in-process specifications may be further purified using the same purification procedure described in the NDA. When an alternate purification procedure is used, the recovered material should be subjected to the same final processing operation and the same testing as for the first time.

FDA recognizes that operating conditions (such as time and temperature) occasionally deviate from the NDA description. A protocol should be provided for the procedure which will be used to qualify the batch of intermediate or drug substance as meeting specifications when reaction conditions or operating parameters fall outside fine typical/normal range (i.e., "excursions," or minor deviations). The protocol should describe the additional analytical testing which will be used in qualification of the batch. The testing should be more extensive than required by routine specifications and tests and may include, as appropriate, the use of nonregulatory analytical methods. For example, batches of new drug substance in this category (i.e., when reaction conditions are outside the norm) should be examined by discerning analytical procedures such as those used for Reference Standard qualification.

In-process control procedures should be established and described for the handling of mother liquors and recovery of second crops when this is done; see section II.D.3.d. While the re-use of mother liquors and recovery of second crops may be common/normal practice and is acceptable from a CGMP viewpoint, it is not necessarily acceptable (i.e., when impurity levels build up), and extensive recycling of mother liquors or repeated recoveries of additional crops is discouraged (refer to section IV (CGMP) and the "Guideline for Inspection of Bulk Pharmaceutical Chemical Manufacture" in this regard.) the recovery procedures should be included in batch production records.

Provision should be made in the NDA for the typical and usual reprocess procedure for drug substance which fails to meet specifications, usually by one or more additional

recrystallizations from the final solvent. Extraordinary analytical examination is not required in this case.

A single batch of drug substance which fails to meet specifications may be purified by an appropriate procedure and then processed by the same final purification procedure described in the NDA, provided that the purity of the reprocessed material being so treated in the final purification step is as good as the normal drug substance at this stage of processing. Some types of bulk drug substance for salvage (e.g., accumulated unused analytical samples, unused portions of lots, bulk returned from customers) may be processed in this fashion.

Such reworked drug substance batches should be subjected to additional analytical examination, as indicated above (i.e., for drug substance resulting from minor deviations of process conditions). The rework operation, and the reason for it, should be documented. The blending of batches or lots for the purpose of salvaging unsatisfactory batches, without subsequent additional purification by an appropriate procedure and processing by the final purification step described in the NDA, is not permitted under current guidelines.

If not part of the original IAA, a supplement should be submitted to the NBA when a standard (validated) reprocessing procedure for unsatisfactory bulk drug substance is to be routinely employed; refer to the "Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing."

When drug substance is to be recovered from dosage forms, reference should also be made to the "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products." This type of operation will require a supplement.

F. Drug Substance Controls

The regulations require specifications and analytical methods (i.e., release controls for the new drug substance) to help assure that the proper identity, strength, quality, and purity of the drug substance have been attained and are consistent from batch to batch. The following information should be submitted to define these specifications and test methods:

1. Sampling

Sampling requirements are covered by CGMP regulations (see section IV). The sampling plan should be described, giving the basis for the plan; it should satisfy appropriate statistical considerations.

2. Release Controls

Examples of specifications and tests that may be applicable are as follows:

a. Appearance/description

b. Physical properties

(e.g., melting range, specific rotation, refractive index, crystalline form, particle size). For drug substances with chiral centers or other configurational requirements, the specifications and tests should assure that material (whether a single enantiomer or isomer, a racemate, or a known ratio of isomers) with the requisite properties for therapeutic activity has been produced. See section III in this regard.

Similarly, when the solid-state properties (see section II.G.) of the new drug substance, such as polymorphism or particle size, are known to affect physiological or pharmacological activity (i.e., bioavailability of the drug product), the specifications and tests should provide appropriate limits for these properties (whether as single forms or as admixtures).

c. Specific identity test(s)

(i.e., infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)). The specific identity tests should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum (KBr pellet) is preferred. Other identity tests (such as UV spectra, or relative mobility [R_f or T_R values] by various chromatographic methods) are considered confirmatory rather than specific. Doing additional (confirmatory) tests is encouraged; however, doing several confirmatory tests will not substitute for a specific identity test.

d. Impurity profile and limits

(i.e., tests to detect, identify, and quantitate the presence of starting materials and intermediates, by-products, degradation products, solvents, and other impurities, as well as proposed/recommended limits for such impurities). Impurities should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort. During the development and validation of the analytical methods the following concerns should be addressed:

- (1) Ability of the method to detect and resolve impurities (i.e., the sensitivity and specificity of the methods);
- (2) Quantitation and linearity of response;
- (3) Nature of the impurity (e.g., starting material, intermediate, degradation product);
- (4) Classification (e.g., major or minor, toxic, known or unknown [i.e., not yet chemically identified or characterized]);
- (5) Isolation, purification, axed proof of structure (i.e., identification and characterization), including the preparation of authentic specimens for comparison when needed. The section on impurities in the application should demonstrate that all the above points have been considered (i.e., that the

examination of the new drug substance for impurities has been adequate, and that reasonable efforts have been made to fully identify and/or characterize them). Structures of known impurities, and validation of the analytical methods, should be provided (following the Specifications and Tests) and be referenced in section II.F.3. (Reference Standard).

All major impurities should be individually limited. The maximum amount per unit dose of every individual impurity should be provided. If there is information on toxicity or information on toxic limits that have been set for these impurities, this information should be provided.

A summary tabulation of the results from the analytical examination of individual batches of the drug substance used in animal and clinical testing, listing all impurities (individually as well as total, and including those which are unidentified), should be provided.

e. Assay

The assay for the drug substance should be specific if possible, since it can then be used for stability-indicating purposes. It may be practical to measure the drug substance and impurities by the same procedure (e.g., high pressure liquid chromatography (HPLC)). Since a specific identity test is required, assay specificity is not essential when impurities which might interfere are controlled (and limited) by suitable (e.g., chromatographic) methods; in these circumstances non-specific assay methods, such as a potentiometric titration, may be employed. The assay limits established in the NDA for the new drug substance, as well as the limits for impurities, should be based on actual manufacturing results (i.e., from analyses of individual batches). A retest date, based on the stability of the compound under actual storage conditions, is desirable.

Microencapsulated compounds should also be tested for particle size and dissolution rate. Not included in this listing, but generally provided as part of the specifications and tests, are (1) moisture content or loss on drying; (2) residue on ignition; (3) residual solvents; (4) heavy metals. The specifications should provide a reasonable material balance.

3. Reference Standard (See Glossary.)

The reference standard can be defined as drug substance of the highest purity reasonably attainable, specifically prepared by independent synthesis or by (further) purification of existing production material, and shown to be authentic material by an extensive set of analytical tests. It is usually used for the structure elucidation work. If the synthesis differs from that in the application, full details should be provided. Any additional purification procedure should be described (see II.D.3.). The reference standard substance is maintained by the applicant as the standard (benchmark) against which working standards are judged.

A working standard is defined as that reference material of known purity used for routine analytical comparison of clinical or production batches of the drug substance and/or drug product.

The analytical testing needed to document the suitability of reference standards is generally more extensive than that required by the bulk drug substance specifications. Appropriate testing procedures may include, where applicable: elemental analysis; various chromatographic methods (e.g., thin layer chromatography (TLC, and HPTLC), high pressure liquid chromatography (HPLC), gas-liquid chromatography (GLC), affinity chromatography, and size exclusion chromatography); infrared (IR) and ultraviolet (UV) spectra; nuclear magnetic resonance spectra (NMR; usually ¹H-NMR and ¹³C-NMR); mass spectrometry (MS); specific rotation (and also optical rotatory dispersion (ORD) and circular dichroism (CD)); X-ray crystallography; phase solubility analysis; thermal analysis methods (e.g., differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetric analysis (TGA)); various methods of radioimmunoassay (RIA); electrophoresis; and bioassay procedures.

The structures of known impurities (e.g., starting materials, process impurities, degradation products) should be shown. The levels of all impurities found (including those not chemically identified, isolated, and characterized) should be provided as a summary tabulation. The validity (i.e., accuracy, precision, sensitivity, specificity) of the analytical methods used for purity determination should be demonstrated. The preparation and characterization of impurity reference standard materials (which are to be submitted for use in methods validation) should also be described. This information may be provided following the section on Specifications and Tests for the new drug substance and referenced in the Reference Standard section.

The data provided in the Reference Standard section for the current batch of a reference standard should include a certificate of test results. Copies of original data (e.g., spectra and chromatograms) from the examination of the reference standard substance, as well as details of interpretation, should be provided.

When the new drug substance has specifications and tests for solid-state forms (see section II.G), the methods for these determinations should be described and the results provided. Reference standards of forms excluded by the specifications, and information on their manufacture and analyses, may be requested.

For replacement batches of reference standards, a certificate of analysis and summary of the analytical profile should be provided demonstrating their suitability for use. (See also the data requirements for samples for methods validation in the "Guideline for Submitting Samples and Analytical Data for Methods Validation" and in 21 CFR 314.50(e)(2)(i)). Since reference standards are essential to testing the bulk substance, their integrity should be safeguarded by proper storage and their stability monitored by periodic examination.

G. Solid-State Drug Substance Forms: Relationship to Bioavailability

The regulations require, where appropriate, specifications characterizing the drug substance so as to assure the bioavailability of the drug product (see 21 CFR 314.50(3)(ii), and 320.52(e)[4-1-85 edition]). Certain solid-state properties of the drug substance (e.g., polymorphic form or amorphism, solvation or hydration, various types of inclusion complexes, and particle size or surface area) may profoundly affect dissolution and bioavailability from solid dosage forms or suspension drug

products. These properties are less important for solution dosage forms and for drug substances which are highly water soluble.

For drug substances with limited aqueous solubility (e.g., griseofulvin, nitrofurantoin), particle size can have a large effect on the behavior of the drug product, and significant differences in particle size may also affect toxicity. Identifying, characterizing, and controlling the differences in solid-state forms is especially important when a bioavailability problem exists and/or the drug substance is obtained from multiple sources.

By the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms, whether these affect the dissolution and bioavailability of the drug product, and whether particle size is important for dissolution and bioavailability of the drug product. It is not necessary to 'create' additional solid-state forms by techniques or conditions irrelevant to the synthetic process.

The applicant should provide information describing how and why it has been concluded that (a) a change in solid-state form does not occur when the drug substance is manufactured and stored according to the NDA directions; or (b) different forms occur but do not result in a bioavailability problem; or (c) polymorphism, solvation, or particle size has an important effect on bioavailability. The test methods used should be briefly described and be shown to be suitable. In cases (a) and (b), suitability means that the procedure(s) can, with reasonable certainty, detect and distinguish between polymorphs (or solvates) should they occur. For case (c), suitability means that the procedure(s) can detect and quantitate polymorphs and/or solvates in admixtures of such forms, or measure particle size.

Appropriate manufacturing and control procedures (including in-process testing when needed) should be established for the production of the desired solid-state form(s). It should be emphasized that the manufacturing process (or storage condition) is responsible for producing particular polymorphs or solvates; the control methods merely determine the outcome.

While specific kinds of differences in solid-state forms are considered separately below, there is some interdependence; thus comparisons should, if possible, be performed on samples of similar particle size.

1. Polymorphism

Some drug substances exist in several different crystalline forms ("polymorphs"), due to a different arrangement of molecules in the crystal lattice, which thus show distinct differences in their physical properties. The same drug substance may also exist in a noncrystalline (amorphous) form. These various forms differ in their thermodynamic energy content, but not in composition. One of the critical factors affecting polymorphism (or solvation) is the choice of final solvent and isolation conditions in the synthesis. As noted previously (II.D.2.d.), when a change is made in the final crystallization solvent, evidence must be provided that no transformation in solid-state form has occurred. Routine storage conditions, as well as some conditions of product manufacture (e.g., tablet compression, or use of an organic solvent during granulation) may also cause transformations. The question is: Is the crystalline (or amorphous) form stable, or is it time and/or process dependent?

Appropriate analytical procedures should be used to determine whether (or not) polymorphism occurs. Some examples of physico-chemical measurements and techniques are (1) melting point (including hot-stage microscopy); (2) infrared spectra (not in solution); (3) X-ray powder diffraction; (4) thermal analysis methods (e.g., differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (MA)); (5) Raman spectroscopy; (6) comparative intrinsic dissolution rate; (7) scanning electron microscopy (SEM). These methods are not ranked in order of their discriminating or quantitating ability. It is the applicant's responsibility to select the method(s) used to provide evidence concerning polymorphism, and if bioavailability is affected, to provide and demonstrate the suitability of the specifications and tests (including preparation and provision of reference standards) for the control of the solid-state form of the drug substance.

2. Solvation (including hydration)

Conditions used in manufacture and/or storage of the drug substance may result in the isolation or formation of a solvated or hydrated drug substance. This is most directly assessed by testing for loss on drying (LOD) or by Karl Fischer titration (for hydrates). Information from other methods (e.g., TGA) may be necessary, because some solvates are known to be stable at temperatures above the boiling point of the solvent. When solvation or hydration affects bioavailability, appropriate manufacturing and control procedures should be established.

3. Particle Size (and surface area)

Particle size distribution and surface area of the drug substance may affect the dissolution and bioavailability of the drug product. Therefore, an applicant may conduct operations to alter particle size/surface area in order to achieve more favorable properties for the drug substance. For drug substances with low aqueous solubility (e.g., less than 5 milligrams per milliliter) both the typical original particle size distribution and the particle size distribution after any alteration procedures should be presented (preferably graphically), with detection limits indicated. The effect of drug substance particle size on dissolution (of the drug product) should also be provided. When particle size/surface area of the drug substance is relevant to the bioavailability of the drug product, the description of the procedures used to alter particle size/surface area and the methods used for examination should be provided, and appropriate specifications and tests established for control.

III. REQUIREMENTS FOR AN INVESTIGATIONAL NEW DRUG (IND)

Present Regulations (21 CFR Part 312) require the submission of manufacturing and controls information for the new drug substance along with the name and address of the manufacturer. Depending on the type of IND and the phase of investigation(s), information should be submitted as described below.

A. New Chemical Entity (see Glossary)

1. Phases 1 and 2

a. Physical and chemical characteristics

The description of the physical and chemical characteristics of the new drug substance (NDS) should include, where applicable, such properties as: appearance, solubility profile, pH/pK, melting point, specific gravity, optical rotation, refractive index, and molecular weight. See also section II.A.1, and 2.

When the NDS is asymmetric (e.g., contains one or more chiral centers, or has cis-trans or other types of isomers), the sponsor should ideally (and prior to the submission of an IND) have either separated the various potential stereoisomers of the NDS or synthesized them independently. Physical/chemical information about each stereoisomer should be provided (in detail), or may be requested. Individual stereoisomers may need to be studied for pharmacological and toxicological properties (and/or for safety and efficacy).

Appropriate specifications and tests to control the ratios of any admixtures (e.g., ratios of enantiomers, and/or solid-state forms) for batches of drug substance used in toxicological and/or clinical studies should be established, so that results can be extrapolated to the drug substance proposed for marketing.

b. Manufacture of the new drug substance (NDS)

A description of the preparation of the NDS (including antibiotics) should include the synthesis, isolation and/or extraction, and purification. This normally should include a flow chart (giving structural formulas, reagents, and catalysts) as well as a written description of the process (on a laboratory/bench scale if that is all the experience available). Pertinent scientific publications or patents should be provided (see Glossary). When significant changes are made in the route of synthesis, or why the scale of the synthesis changes considerably (as from bench to pilot plant), the IND should be updated accordingly (by amendment in the case of route change; by annual report otherwise).

c. Analytical methods

The analytical methods for the NDS should include at least one specific identity test, one or several impurity tests (preferably some type of chromatographic examination), and an assay procedure. It is recognized that any limits set are tentative.

The elucidation of the structure of the reference I standard material, or the authentic substance, should be documented to the extent possible at this stage (see section II.F.3.). It is recognized that this may not be feasible for certain complex substances (e.g., products of natural origin), but adequate efforts should be made to characterize such substances.

2. Phase 3

a. Manufacture of the new drug substance

The manufacturing procedure for the NDS should be fairly well established by the latter part of this stage of development. A description of the process should be submitted, in sufficient detail to approach the NDA requirements (see section II.D.). Alternate synthetic pathways/routes employed to prepare batches used in clinical trials should also be described. The sponsor may continue to modify; revise, or even totally change the synthesis; such changes should be reported accordingly (as amendments, or in the periodic report as warranted).

b. Analytical methods

The sponsor should appropriately update the controls and revise the specifications for the NDS when extensive (Phase 3) studies are to be initiated. Before or early in Phase 3, it is expected that all major impurities will have been isolated and identified. Levels of impurities, either individual or total, should be controlled. Information regarding stereochemistry and its relation to pharmacological and toxicological activities may also be requested if not already provided (as requested for Phase 1 and Phase 2 studies). It is also expected that studies of any solid-state forms) of the NDS (and their relevance to bioavailability of the drug product) will have been conducted or initiated during the Phases 1 and 2 studies, and appropriate specifications developed (if not already provided).

As Phase 3 studies progress, the cumulative manufacturing and controls information should be updated at suitable intervals. Sponsors should consider preparation of the samples (including impurity samples) and information required for the NBA validation package, and perhaps also consider a pre-NDA manufacturing and controls submission.

B. Known Chemical Entity (see Glossary)

1. Sponsor-Investigator Research Study (documentation on file)

The sponsor of a research study can comply with the manufacturing and controls information requirements by requesting the manufacturer of the drug substance or drug product to authorize the agency to refer to a DMF, IND, or NDA.

When a sponsor-investigator either prepares the dosage form(s) himself from a commercially obtained drug substance (known chemical entity) or modifies the drug product, refer to the "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products" for the information required.

A sponsor-investigator is advised to contact the agency why a drug substance itself is to be altered before making dosage forms (e.g., as in the case of conversion of a salt to the free base or acid, or to a different salt).

2. Sponsor-Investigator Research Study or Commercial Sponsor (no documentation on file)

The sponsor of a research study with a drug substance for which the agency does not have documentation on file can comply with the regulations by submitting the following:

- a. Best available descriptive name and chemical structure of the NDS;
- b. Statement of the source of the NDS, including name and address of the manufacturer;
- c. A description of the preparation of the NDS, including (when possible) diagrammatic flow charts of the chemical reactions used in the synthetic process;
- d. A description of the methods which will be used to determine that the identity, strength, quality, and purity of the NDS is initially adequate and will be maintained for the duration of the clinical trial. The sponsor may rely on the manufacturer's results (i.e., the Certificate of Analysis, and stability studies) to satisfy this requirement, provided that the sponsor performs a specific identity test for acceptance.
- e. The information requested above should be accompanied by appropriate scientific literature references.

If an NDA for this type of study is submitted, the review of the NDA could be delayed if the description of the method of manufacture of the known chemical entity is not on file (IND, DMF, etc.).

IV. CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS (CGMP'S)

Bulk pharmaceutical chemicals (BPC's) are the active and inactive components used by the pharmaceutical industry in the formulation of finished drug products. This includes any substance that is relabeled or repackaged for drug use. Section 201(g) of the Federal Food, Drug, and Cosmetic Act (the act) defines BPC's as drugs; therefore they must meet all requirements set forth in the act as well as all pertinent regulations. Since there are no specific regulations for the production of BPC's, the Commissioner has stated in the preamble to the CGMP regulations for finished drug products that these regulations will be used as guidance for the manufacture of BPC's.

For more specific GMP Requirements, including homogeneity and sampling, refer to the document "Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing."

Some aspects of manufacturing practice have been considered in Section II.E. (Process Controls) of this Guideline; information about these areas should be provided in NDA submissions.

GLOSSARY

1. Drug Substance An active ingredient, intended for incorporation into a finished dosage form, that meets the statutory definition of a drug (i.e., 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).
2. Drug Product A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally but not necessarily in association with one or more other ingredients.
3. Pivotal Intermediate An intermediate that is permitted to be prepared by several different synthetic routes (or fermentation procedures). Pivotal intermediates are not common in syntheses because the definition requires that there be two or more distinct and independent methods for their synthesis. Ordinary late-stage intermediates do not meet the definition, regardless of their importance to the success of the synthesis (i.e., "Pivotal" does not necessarily mean "vital").
4. Key Intermediate An intermediate in which an essential molecular characteristic(s), usually involving the proper stereochemical configuration required for structure/activity (pharmacological and/or physiological activity of the drug substance), is first introduced into the structure (e.g., introduction of a chiral center, as exemplified by the Corey aldehyde in prostaglandin syntheses, or the production of one geometric isomer in preference to another).
5. In Situ Intermediate An intermediate that is not isolated. It is normally but not necessarily in solution.
6. Final Intermediate By definition this is the last compound synthesized before the reaction that produces the new drug substance. The final step, forming the new drug substance, must involve covalent bond formation. However, formation of simple esters (e.g., methyl, ethyl, etc.) does not qualify as the final synthetic step, so that the precursor to the unesterified acid is the final intermediate. Complex esters (where both the alcohol and the acid result from several-step syntheses) are acceptable. Ionic bond formation (i.e., making the salt of a compound) does not qualify; thus, when the drug substance is a salt, the precursors to the organic acids or bases should be considered as the final intermediate rather than the acid or base themselves. There may be more than one final intermediate depending on the nature of the synthesis (e.g., parallel or shotgun routes, where two or more major fragments leading to the final molecule are combined).
7. Reference Standard A particular lot or batch of drug substance specifically prepared, either by independent synthesis or by additional purification of production material, and shown, by an extensive set of analytical tests, to be authentic material of the highest purity reasonably attainable. It is usually used for structural elucidation, and is the benchmark for working standards.
8. Working Standard Drug substance of established quality and purity as shown by comparison to the Reference Standard material, used as a standard substance for routine laboratory work, as in analyses of production batches of new drug substance or drug product(s).
9. Known Chemical Entity A chemical which has been adequately characterized in the literature with regard to its physical and chemical properties.
10. New Chemical Entity A chemical which has not been adequately characterized in the literature with regard to its physical and chemical properties. (Not to be confused with "New Molecular Entity".)

11. Major impurity One that is important either because of the quantity present or because of its toxicity.
12. New Molecular Entity (NM) A term used by the FLT to describe the subject of a drug application (IND or NDA) classified as Chemical Type 1 (i.e., an active moiety not yet marketed in the U. S. A.).
13. Chemical Literature This refers to complete published journal articles, patents, and texts, as indexed by chemical Abstracts. The FDA Medical Library does not receive all journals. Copies of articles and patents should be provided to expedite review, with English translations as required. Recent issues of major American chemistry journals (e.g., Journal of Medicinal Chemistry) need not be provided