Guidance for Industry

INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products

Chemistry, Manufacturing, and Controls Content and Format

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 1999
CMC

Draft – Not for Implementation

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GUIDANCE FOR INDUSTRY[1]

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(Due to the complexity of this draft document,please identify specific comments by line number. Use the pdf version of the document whenever possible.)

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors of investigational new drug applications (INDs) on the chemistry, manufacturing, and controls documentation (CMC), including microbiology documentation, that should be submitted for phase 2 and phase 3 studies conducted under INDs.[2] This document applies to human drugs (as defined in the Federal Food, Drug, and Cosmetic Act) and specified biotechnology-derived products (as defined in 21 CFR 601.2). The guidance does not apply to botanical drug products, vaccines, immune sera, blood products, or allergenics. The goals of the guidance are to (1) facilitate drug discovery and development, (2) ensure that sufficient data will be submitted to the Agency to assess the safety as well as the quality of the proposed clinical studies from the CMC and microbiology perspectives, and (3) expedite the entry of new drugs into the marketplace. Although applicable to both commercial- and individual investigator-sponsored IND applications, the document's greater value and relevance will be for commercial IND applications.

The amount and depth of CMC information that should be submitted to the Agency depends, in large part, on the phase of the investigation and the specific testing proposed in humans. This guidance reflects current Agency thinking regarding CMC submissions for phase 2 and 3 studies conducted under an IND.

The recommendations in this guidance provide regulatory relief for IND sponsors in three specific areas. First, the phase 3 supplementary data and information corroborating the quality and safety criteria established in earlier investigational phases need not be submitted before the initiation of

[1] This guidance has been prepared by IND Reform Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on CMC content and format of INDs for phase 2 and 3 studies of human drugs, including specified therapeutic biotechnology-derived products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] Recommendations will be provided in other guidances for CMC issues relating to pre-IND, at the end of phase 2 (EOP2), and pre-new drug application (NDA)/biologics license application (BLA) meetings (drafting), and pre-NDA/BLA rolling submissions (guidance for industry on *Fast Track Drug Development Programs - Designation, Development, and Application Review*, November 17, 1998).

phase 3 studies and can be generated during phase 3 drug development. This should provide the sponsor with greater flexibility. Second, a sponsor may elect to delay submitting data elements obtained in earlier investigations until phase 3 if they do not affect safety. This allows sponsors to postpone the submission of data and information, even if generated before and during earlier investigational phases. Third, a sponsor may submit summary reports annually and does not need to resubmit data and information already submitted. Redundant submissions of data and information are thus avoided.

For phase 1 submissions, sponsors should refer to the November 1995 guidance for industry *on Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995).

II. BACKGROUND

A. Current Requirements

Under current regulations in the United States, use of a drug product not previously authorized for marketing in the United States requires the submission of an IND to the Agency. FDA's regulations at 21 CFR 312.22 and 21 CFR 312.23 contain the general principles underlying the IND submission and the general requirements for content and format. Regulations at 21 CFR 312.23(a)(7)(i) require that each phase of investigation include sufficient CMC information to ensure the proper quality, identity, purity, and strength of the drug substance and drug product. The type of information submitted will depend on the phase of the investigation, the extent of human study, the duration of the investigation, the nature and source of the drug substance, and the dosage form of the drug product.

B. General Principles

The recommendations in this guidance on CMC information focus on the safety issues relating to phase 2 and phase 3 studies. In addition, recommendations are provided regarding supplementary data and information for phase 3 (21 CFR 312.22) that corroborate the quality and safety criteria established in earlier investigational phases. Corroborating data and information specified in Section IV (Phase 3/Pivotal Study) that are generated earlier in phase 1 and phase 2 need not be submitted until the initiation of phase 3 studies. If these data are not generated in phase 1 or phase 2, they can be submitted at the time they are generated during phase 3. Section IV of this guidance is entitled Phase 3/Pivotal Study to emphasize that the corroborating data and information specified in that section need not be submitted before initiating phase 3 studies.

All updates or revisions of the CMC section during phase 2 and phase 3 (e.g., manufacturing process, formulation, tests, specifications) should be submitted in accordance with 21 CFR 312.31 (information amendments) and 21 CFR 312.33 (annual reports). In general, CMC safety information and data and CMC safety updates should be submitted during IND clinical trials as information amendments. The information

specified in the Phase 3/Pivotal Study section can be submitted as summary annual reports if the changes do not affect safety. If the change in phase 3 could affect safety, the information should be reported in an information amendment. CMC modifications that may affect safety include, but are not limited to, a change in the method of sterilization, a change in container/closure system affecting product quality, a change in synthesis resulting in different impurity profiles, or a change from synthetic to biological source (human or animal) of a drug substance.

As clinical development of the drug product proceeds, sponsors should discuss with the Agency the type of manufacturing data that should be submitted to support the safe use of the drug in all investigational phases. The Agency encourages sponsors to meet with the CMC review team prior to the initiation of pivotal clinical trials to discuss issues and protocols that might affect the approvability of the NDA.

III. PHASE 2

IND submissions filed during phase 2 should contain chemistry, manufacturing, and controls information in accordance with 21 CFR 312.23(a)(7). The CMC information provided to support the phase 2 studies should focus on (1) updated phase 1 information (see November 1995 phase 1 guidance, section III.F) and (2) additional information relating to phase 2 safety issues. The information below outlines information beyond that recommended for phase 1 studies that should be submitted in support of phase 2 studies. In cases where studies begin with phase 2 clinical studies, CMC safety information should be submitted as specified in the November 1995 phase 1 guidance and in this section.

A. Drug Substance

Sponsors can reference the current edition of the *United States Pharmacopeia/National Formulary* (USP/NF) to provide the recommended CMC information for an investigational drug substance, when applicable. Reference to drug master files (DMFs) with an authorization letter by the DMF holder can also be used to provide CMC information in support of the IND submission (21 CFR 314.420).

1. Characterization and Description

Safety updates on information identified in the November 1995 phase 1 guidance (i.e., a brief description of the drug substance and some evidence to support its proposed chemical structure) should be provided, with a more detailed description of the configuration and chemical structure for complex organic compounds.

2. Manufacturer

The addition, deletion, or change of any manufacturer of the drug substance reported during phase 1 should be identified.

3. Synthesis/Method of Manufacture and Controls

The structure of the starting materials and information to support the classification of a compound as a starting material should be provided (see FDA's *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, February 1987). The source, methods, and test results for the starting materials should be available on request. For specified therapeutic-biotechnology derived products, cell lines should have been described and cell banks characterized in phase 1. and changes in cell lines/cells should be submitted in updates. For natural products extracted from human or animal sources, the origin of the starting materials and details of appropriate screening procedures for adventitious agents should have been described in phase 1.

Safety updates on reagents, solvents, auxiliary materials, and proposed changes identified during phase 1 should be provided. The general description of the synthetic and manufacturing process (e.g., cloning, cell banks, fermentation, purification) described in the November 1995 phase 1 guidance should be updated from a safety perspective if changes or modifications have been introduced. Reprocessing procedures and pertinent controls need not be described.

An updated detailed flow diagram for the synthesis or manufacturing process should be provided. When feasible, the flow diagram should contain the chemical structures and configurations, including stereochemical information of the starting materials, intermediates (either in situ or isolated), and significant side products. Reagents (including solvents and catalysts), equipment (e.g., fermenters, columns), and provisions for monitoring and controlling conditions used in each step should be identified.

During the clinical investigation process, the sponsor should be developing tentative acceptance criteria that are continually refined based on data obtained from analysis of batches of drug substance and new information that becomes available. To the extent possible in phase 2, sponsors should document that the manufacturing process is controlled at predetermined points and yields a product meeting tentative acceptance criteria. Although in-process controls may still be in development, information on in-process controls for monitoring adventitious agents should be provided for biotechnological drug substances, as appropriate.

4. Reference Standard

A national or international reference standard may not be available because many IND applications will be for new molecular entities. In this case, the sponsor can select a batch to be used as a reference material, against which initial clinical batches are tested prior to their release. Preferably, the sponsor should establish a working standard even at the initial stage of drug development. A *working standard* is a reference material that has been further characterized beyond the standard batch release tests. When a reference material is fully characterized, it becomes the manufacturer's primary reference material. The manufacturer can continue to establish new working standards that are calibrated against that primary reference material. Where a recognized national or international

standard (primary standard) is available, the manufacturer's reference material and/or working standard should be calibrated against this standard.

5. Specification

A *specification* is a list of tests, references to analytical procedures, and acceptance criteria (i.e., numerical limits, ranges, or other criteria for the tests described). Each critical quality attribute, such as identity, purity, quality, potency/strength, product-related impurities, and process-related impurities, can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, the analytical technology often evolves parallel to the clinical investigations. In setting subsequent NDA/BLA acceptance criteria, relevant correlations should be established between data generated during early and late drug development.

Any changes in the specification should be reported. The analytical procedure used to perform a test and to support the acceptance criteria should be indicated (e.g., HPLC). A complete description of the analytical procedure and supporting validation data should be available on request. Any changes in the tentative acceptance criteria should be stated. Test results, analytical data, and certificates of analysis (COA) of clinical trial material prepared since the filing of the original IND should be provided.

6. Container Closure System

A brief description of any changes in the container closure system (also referred to as the packaging system) should be provided. The *container closure system* is defined as the sum of packaging components that together contain and protect the drug substance.

7. Stability

If degradation of the drug substance (or drug product) occurs during manufacture and storage, this should be considered when establishing acceptance criteria and monitoring quality. Due to the inherent complexity of many drug substances, there is no single stability-indicating assay or parameter that profiles all the stability characteristics of all substances or products. Consequently, the manufacturer should propose stability-indicating analytical procedures that will detect significant changes in the quality of the drug substance. The particular drug substance will determine which tests should be included.

Performance of stability stress studies with the drug substance early in drug development is encouraged, as these studies provide information crucial to the selection of stability-indicating analytical procedures for real time studies.

A stability protocol should be submitted that includes a list of tests, analytical procedures, sampling time points for each of the tests and the expected duration of the stability program. Preliminary stability data based on representative material should be provided. All stability data for the clinical material used in the phase 1 study should be provided.

B. Drug Product

Sponsors can reference the current edition of the USP/NF to provide the recommended CMC information for investigational drug products, when applicable. Reference to DMFs with an authorization letter by the DMF holder may be used to provide CMC information in support of the IND submission (21 CFR 314.420).

1. Component/Composition/Batch Formula

Any changes to the information specified for phase 1 (i.e., table listing of all components) should be provided. The components should be identified by their established names and compendial status, if they exist. In addition, quantitative composition per unit of use should be provided (e.g., mg/tablet or mL). A batch formula should be provided, if not already submitted. The formulation for certain drug products delivered by devices (e.g., metered dose inhalers (MDIs), dry powder inhalers (DPIs), nasal sprays) should be similar to that intended for the marketed drug product.

2. Specifications for Components

Changes in acceptance testing for active ingredients submitted during phase 1 should be provided. For excipients, the quality (e.g., USP, NF) of the excipients should be specified if changed.

Analytical procedures and acceptance criteria should be provided for noncompendial components. A brief description of the manufacture and control of these compounds or an appropriate reference should be provided (e.g., DMF, NDA, BLA). Information for excipients not included in previously approved drug products should be equivalent to that submitted for new drug substances.

3. Manufacturer

Updates on the information specified in the November 1995 phase 1 guidance should be provided.

4. Method of Manufacturing, Packaging and Process Controls

A brief, step-by-step description of the manufacturing procedure for the unit dose should be provided. The description should focus only on the general manufacturing task (e.g., milling). Flow diagrams should be included. Information does not need to be provided for the following: (1) specific equipment used (e.g., V-blender); (2) the packaging and labeling process, and (3) in-process controls, except for sterile products (e.g., injectables, implants, ophthalmics) or atypical dosage forms (e.g., MDI, liposomal encapsulation, implants, injectable microspheres). Only safety related information need be submitted for reprocessing procedures and controls.

For sterile products, safety updates on the manufacturing process information filed for phase 1 studies should be submitted. The phase 2 information should include changes in

the drug product sterilization process (e.g., terminal sterilization to aseptic processing) or other changes introduced in the process to sterilize bulk drug substance or bulk drug product, components, packaging, and related items. Information related to the validation of the sterilization process need not be submitted at this time.

5. Specification

Changes to the specification should be reported. Chemical tests (e.g., dissolution, identity, assay, content uniformity, impurities) and microbiological tests (sterility and endotoxin/LAL for sterile products; antimicrobial preservative and microbial limits for non-sterile dosage forms) that were added, deleted, or changed since phase 1 should be indicated. The analytical procedure used to perform a test and support the acceptance criteria should be indicated (e.g., HPLC). The complete description of the analytical procedure and supporting validation data should be available upon request. Any changes in tentative acceptance criteria should be stated for each test performed.

Data updates on the degradation profile should be provided so safety assessments can be made. A summary table of the test results, analytical data (e.g., chromatogram), and COA for lots of the drug product used in clinical studies should be provided.

6. Container Closure System

A brief description of any changes in the container closure system (also referred to as packaging system) should be provided. The *container closure system* is defined as the sum of packaging components that together contain and protect the drug product. The container closure system of certain drug products delivered by devices (e.g., MDIs, DPIs, and nasal sprays) should be similar to that intended for the marketed drug product.

7. Stability

A stability protocol should be submitted that includes a list of the tests, analytical procedures, sampling time points for each of the tests, and the expected duration of the stability program. As in phase 1, the stability of the reconstituted solution, when applicable, should be studied and data provided. Preliminary stability data should be based on representative material. All available stability data for the clinical material used in phase 1 study should be provided. Stress testing (e.g., photostability) on the drug product should be conducted.

IV. PHASE 3/PIVOTAL STUDY

A. Drug Substance

Sponsors can reference the current edition of the USP/NF to provide the recommended CMC information for investigational drug substances, when applicable. Reference to drug

master files (DMFs) with an authorization letter by the DMF holder may be used to provide CMC information in support of the IND submission (21 CFR 314.420).

1. Characterization and Description

A complete description of the physical, chemical, and biological characteristics of the drug substance should be provided, including elements such as (1) neutralization equivalents, (2) solubility properties, partition coefficient, dissociation constant (pK), and isoelectric point (pI), (3) hygroscopicity, (4) crystal properties and morphology determined by thermal analysis (e.g., DSC, TGA),[3] powder X-ray diffraction and microscopy, (5) particle size and surface area, (6) melting point and boiling point, (7) specific rotation, (8) stereochemistry, (9) Ig class for immunoglobulins, and (10) biological activities (when applicable).

Supporting evidence to elucidate and characterize the structure should be provided and can include elemental analysis, conformational analysis, molecular weight determination, spectra from IR, NMR (^{1}H & ^{13}C), UV, MS, optical activity, and single crystal X-ray diffraction data, if available.[4] For peptides and proteins, characterization should include data on the amino acid sequence, peptide map, post-translational modifications (e.g., glycosylation, gamma carboxylation), and secondary and tertiary structure information, if known.

2. Manufacturers

A list of all firms associated with the manufacturing and controls of the drug substance should be provided, including contract laboratories for quality control and stability testing.

3. Synthesis/Method of Manufacture and Controls

In addition to the information provided during phases 1 and 2, updates of the acceptance criteria and analytical procedures for assessing the quality of starting materials should be provided. A table listing all reagents, solvents, and catalysts should be submitted that includes (1) the grade of each material used, (2) the specific identity test performed, (3) the minimum acceptable purity level, and (4) the step of the synthesis and manufacturing process in which it is used. For special reagents (e.g., reagents for kinetic resolution, sera, enzymes, or proteins of animal origin), a more comprehensive list of tests, screening, and acceptance criteria may be needed. In critical cases (e.g., monoclonal antibodies configured in affinity matrices), a full description of the manufacturing process may also be needed.

An updated detailed flow diagram should be provided and should contain the chemical structures and configuration including stereochemical information of the starting materials,

[3] Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

[4] Infrared spectrometry (IR), nuclear magnetic resonance spectrometry (NMR), ultraviolet spectrometry (UV), and mass spectrometry (MS).

intermediates (either in situ or isolated), and significant side-products. Reagents (including solvent and catalyst), equipment (e.g., fermenters, columns), and monitored and controlled conditions used in each step should be identified.

A general step-by-step description of the synthesis and manufacturing processes, including final recrystalization of the drug substance should be provided. Relevant information should indicate the batch size (range), the type of reaction vessel, the relative ratios of reactants, catalyst, and reagents, general operating conditions (time, temperature), in-process controls (complete description of the analytical procedures), and literature references for any novel reactions or complex mechanisms. For specified biotechnology-derived products, validation of the genetic stability of the cells in production, with defined passage limits, should be performed.

Controls at selected stages in the synthesis or manufacturing process that ensure reaction completion, identity, and purity or proper cell growth should be described. The acceptance criteria and analytical procedures should be described for isolated intermediates that require control. Tentative acceptance criteria can be used to allow for flexibility in the development process, but should fulfill the primary purpose of quality control. The description of the analytical procedures should be brief, and appropriate validation information should be available on request. Reprocessing procedures and pertinent controls should be described.

4. Reference Standard

If a national or international standard is not yet available, the sponsor should establish its own primary reference material during phase 3 studies. The manufacturer can continue to use the working standard used in phase 2 or can establish a new working standard for lot release. The synthesis and purification of the reference material or working standard used should be described if it differs from that of the investigational drug substance. The analytical procedures and calibration results for the working standard against the primary reference material should be provided. Additional analytical procedures used to characterize the working standard and the primary reference material should be updated in the Characterization and Description section of the submission (III.A). Where a recognized national or international standard (primary standard) is available and appropriate, the manufacturer's reference material and/or working standard should be calibrated against this standard, and the results provided.

5. Specification

A detailed listing of all the tests performed (e.g., description, identity, assay, loss on drying) should be provided. A general description of the analytical procedures should be provided that includes a citation to the specific USP monograph or general chapter or the sponsor's standard test procedure number, as appropriate. A complete description of the non-USP analytical procedures with appropriate validation information should be provided. The assay validation program should be designed to delineate various analytical parameters such as accuracy, precision, and specificity, as well as detection limits, quantitation limits, linearity, and range, where appropriate (see the FDA *Guideline for*

Submitting Samples and Analytical Data for Methods Validation, February 1987). Tentative acceptance criteria should be established for each test performed.

Impurities should be identified, qualified, and quantified, as appropriate. Suitable limits based on manufacturing experience should be established. Suitable microbial limits should be established for nonsterile products and changes in previously reported limits should be reported.

A summary table of updated test results, analytical data (e.g., IR spectra, HPLC chromatograms, microbial limits for incoming raw materials prior to sterilization) and COAs for the lots of drug substance used in clinical trials should be provided.

6. Container Closure System

The container closure system used to transport and/or store the bulk drug substance should be described in detail. This container closure system should be simulated in the drug substance stability studies.

7. Stability

If not performed during phase 2 studies, stress studies should be conducted to demonstrate the inherent stability of the drug substance, potential degradation pathways and the capability and suitability of the proposed analytical procedures. This one-time study on a single batch is not considered part of the normal stability protocol. The stress study should assess the stability of the drug substance in various pH solutions, in the presence of oxygen and light, and at various elevated temperature and humidity increments.

The stability protocol submitted should include a detailed description of the drug substance under investigation, its packaging, a list of the tests to be conducted, analytical procedures to be used, sampling time points for each test, temperature/humidity conditions to be studied, and the expected duration of the accelerated and long-term testing program. Tabulated data should be presented and should include the lot number, manufacturing site, and the date of manufacture of the drug substance lot. Each table should contain data from only one storage condition. Individual data points for each test should be reported. Representative chromatograms and spectra should be provided, when applicable.

A short description should be provided for each parameter being investigated in the stability program studies (i.e., stress, long-term, and accelerated studies) demonstrating that appropriate controls and storage conditions are in place to ensure the quality of the drug substance used in clinical trials. Tests unique to the stability program should be adequately defined and described.

B. Drug Product

Sponsors can reference the current edition of the USP/NF to provide the recommended CMC information for investigational drug products, when applicable. Reference to DMFs

with an authorization letter by the DMF holder can be used to provide CMC information in support of the IND submission (21 CFR 314.420).

1. Components, Composition, and Batch Formula

The sponsor should provide updated information regarding the components, composition, and batch formula for phases 1 and 2. Components that are removed during the manufacturing of the drug product should be listed, but quantitative values do not need to be reported. Quantitative information should be reported for the batch formula. The formulation for certain drug products delivered by devices (e.g., MDIs, DPIs, and nasal sprays) should be similar to that intended for the marketed drug product.

2. Specifications for Components

Updates on the acceptance testing of the drug substance should be provided. Analytical procedures and acceptance criteria established for the drug substance by the drug product manufacturer, if different, should be described in the drug substance section of submissions.

Updates on compendial excipient information specified for phase 2 should be provided. In certain cases, additional testing (e.g., functionality) may be useful and should be proposed. For a noncompendial excipient, updates and a full description of the characterization, manufacture, control, analytical procedures, and acceptance criteria should be provided. Alternatively, a reference with authorization to a DMF can be provided.

3. Manufacturers

A listing of all firms associated with the manufacturing and controls of the drug product should be submitted, including the contractors for stability studies, packaging, labeling, and quality control release testing.

4. Method of Manufacturing, Packaging, and Process Controls

A general step-by-step description of the manufacturing method for a unit dose should be provided, including key equipment employed. Where the qualitative formulation does not change, a single description of the manufacture of different strength unit doses can be used. The description should indicate how the material is being processed and can be general enough to allow for flexibility in development. In planning the clinical batch size, the sponsor should consider the postapproval production scale. A brief description of the packaging and labeling process for clinical supplies should be provided. Reprocessing procedures and pertinent controls should be described, if applicable.

For sterile products, updates on information specified for phases 1 and 2 should be provided. The information should include a description of changes in the drug product sterilization process (e.g., terminal sterilization to aseptic processing) or other changes introduced into the process to sterilize bulk drug substance or bulk drug product, components, packaging, and related items. Information related to the validation of the

sterilization process need not be submitted at this time, but should be submitted at the time of an NDA or BLA filing (see FDA guidance for industry *Sterilization Process Validation*, November 1994).

5. Specification

Updates on the information specified for phases 1 and 2 should be provided. A general description of the analytical procedures used should be provided that includes a citation to the specific USP monograph, general chapter, or the sponsor's standard test procedure number, if appropriate. A full description of the non-USP analytical procedures with appropriate validation information should be provided. The acceptance criteria should be stated for each test performed. Degradation products should be identified and qualified.

For sterile preserved products in multiple dose containers, a citation to the USP Antimicrobial Preservative-Effectiveness Test (APET) or a description of an equivalent procedure with the associated test validation information should be provided. This test should be performed at the lowest specified concentration of antimicrobial preservative specified for the drug product at release or at the end of the expiration dating period, whichever is less. The efficacy of preservative systems is judged by their effect on inoculated microorganisms.

6. Container Closure System

Updates on the information previously filed should be submitted. In addition, the name of the manufacturer and supplier should be provided. If the component meets USP criteria, it should be stated (e.g., Type I glass). A DMF reference and authorization should be provided, if available. Additional information may be recommended for atypical delivery systems (e.g., MDIs, disposable injection devices). The container closure system of certain drug products delivered by devices (e.g., MDIs, DPIs, and nasal sprays) should be similar to that intended for the marketed drug product.

7. Stability

One-time stress studies should be conducted and results demonstrating the inherent stability of the drug product, potential degradation products, and the capability of the analytical procedures should be included. These one-time studies should also examine the stability of the drug product in the presence of light.

The stability protocol should include a description of the drug product under investigation in the stability program, a description of the packaging, a list of the tests, sampling time points for each of the tests, temperature and humidity conditions to be studied, expected duration of the stability program, and the proposed bracketing/matrixing protocol, if applicable. Dissolution profiling in physiologically relevant media with reasonable speeds of agitation should also be included, where appropriate. The specific analytical procedures should be referenced to the drug product specification section of the IND application or the USP, if possible.

A detailed data table that includes the lot number, manufacturing site, the date of manufacture of the drug product, and the drug substance used to manufacture the lot should be provided. Each table should contain data from only one storage condition. Individual data points for each test should be reported. Representative chromatograms should be provided, if applicable.

A short description should be provided for each of the parameters being investigated in the stability program (i.e., stress, long-term, and accelerated) demonstrating that the appropriate controls and storage conditions are in place to ensure the quality of the product used in clinical trials. Tests unique to the stability program should be adequately defined.

For sterile products, the sponsor should consider the development of a container closure challenge test for future stability protocols. An appropriately designed test demonstrates that the container closure system can maintain the integrity of the microbial barrier during drug product shelf life. A discussion of how the selected test relates to the integrity of the container should be provided.

V. PLACEBO

In addition to the information provided during phase 1, data demonstrating the absence of the active ingredient should be provided for phases 2 and 3.

VI. LABELING

Updates on the information filed for phase 1 should be provided during phases 2 and 3.

VII. ENVIRONMENTAL ASSESSMENTS

Updates on information already submitted and whether a claim for a previous categorical exclusion has changed should be provided during phases 2 and 3 (see FDA guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*, July 1998).

RESOURCES

Although not intended to be applicable to IND applications, the International Conference on Harmonisation (ICH) documents below can serve as valuable resources in guiding the course of product development.

ICH Guidances

ICH Q1A *Stability Testing of New Drug Substances and Products,* September 1994.

ICH Q1B *Photostability Testing of New Substances and Products,* May 1997.

ICH Q1C *Stability Testing of New Dosage Forms,* November 1996.

ICH Q2A *Validation of Analytical Procedures,* March 1995.

ICH Q2B *Validation of Analytical Procedures: Methodology*, November 1996.

ICH Q3A *Impurities in New Drug Substances,* January 1996.

ICH Q3B *Impurities in New Drug Products,* May 1997.

ICH Q3C *Guidance on Impurities: Residual Solvents*, December 1997.

ICH Q5A *Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*, March 1997.

ICH Q5B *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Proteins Products*, February 1996.

ICH Q5C *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, July 1996.

ICH Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products,* Draft, May 1997.

ICH Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products,* Draft, June 1998.

ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,* Draft, November 1997.

FDA Guidances for Industry

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, November 1995.

Environmental Assessment of Human Drug and Biologics Applications, July 1998.

Fast Track Drug Development Programs - Designation, Development, and Applications Review, November 1998.

Submitting Samples and Analytical Data for Methods Validation, February 1987.

Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, February 1987.

Sterlization Process Validation, November 1994.