

# **Guidance for Industry**

## **CGMP for Phase 1 Investigational Drugs**

**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)  
Office of Regulatory Affairs (ORA)**

**July 2008  
CGMP**

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## CGMP for Phase 1 Investigational Drugs

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## **Guidance for Industry CGMP for Phase 1 Investigational Drugs<sup>1</sup>**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### **I. INTRODUCTION**

This guidance is intended to assist in applying current good manufacturing practice (CGMP) required under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in the manufacture of most investigational new drugs (IND) used in phase 1 clinical trials.<sup>2</sup> These drugs, which include biological drugs, are exempt from complying with 21 CFR part 211 under 21 CFR 210.2(c) (referred to as phase 1 investigational drugs).

Because a phase 1 clinical trial initially introduces an investigational new drug into human subjects, appropriate CGMP help ensure subject safety. This guidance applies, as part of CGMP, quality control (QC) principles to the manufacture of phase 1 investigational drugs (i.e., interpreting and implementing CGMP consistent with good scientific methodology), which foster CGMP activities that are more appropriate for phase 1 clinical trials, improve the quality of phase 1 investigational drugs, and facilitate the initiation of investigational clinical trials in humans while continuing to protect trial subjects.

This guidance replaces the guidance issued in 1991 titled *Preparation of Investigational New Drug Products (Human and Animal)* (referred to as the 1991 guidance) (Ref. 1) for the manufacture of phase 1 investigational drugs described in this guidance (see section III). However, the 1991 guidance still applies to the manufacture of investigational new products (human and animal) used in phase 2 and phase 3 clinical trials.

The guidance finalizes the draft guidance entitled “INDs—Approaches to Complying with CGMP During Phase 1” dated January 2006; and is being issued concurrently with a final rule that specifies that 21 CFR part 211 no longer applies for most investigational products (see section III), including certain exploratory products (Ref. 2) that are manufactured for use in

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<sup>1</sup> This guidance has been prepared by an Agency working group with representatives from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA), at the Food and Drug Administration.

<sup>2</sup> See 21 CFR 312.21(a)

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phase 1 clinical trials. The agency recommends using the approaches outlined in this guidance for complying with § 501(a)(2)(B) of the FD&C Act.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

### **A. Statutory and Regulatory Requirements**

Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351 (a)(2)(B)) requires drugs, which include IND products, to comply with current good manufacturing practice as follows:

A drug...shall be deemed adulterated...if...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Based on the statutory requirement for manufacturers to follow CGMP, FDA issued CGMP regulations for drug and biological products (see 21 CFR parts 210 and 211). Although FDA stated at the time of issuance that the regulations applied to all types of pharmaceutical production,<sup>3</sup> the preamble to the regulations indicated that FDA was considering proposing additional regulations governing drugs used in investigational clinical trials.

Because certain requirements in part 211, which implement § 501(a)(2)(B) of the FD&C Act, were directed at the commercial manufacture of products typically characterized by large, repetitive, commercial batch production (e.g., those regulations that address validation of manufacturing processes (§ 211.110(a)), and warehousing (§ 211.142)), they may not be appropriate to the manufacture of most investigational drugs used for phase 1 clinical trials.

Section 505(i) of the FD&C Act (21 U.S.C. 355(i)) directs the Secretary of Health and Human Services to promulgate regulations for exempting from the operation of section 505 "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." Based on this statutory mandate, among

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<sup>3</sup> Preamble to the CGMP 1978, comment #49. "The Commissioner finds that, as stated in 211.1, these CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages. It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production. The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages."

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others, FDA has issued regulations governing IND products to protect human subjects enrolled in clinical trials. For example, in part 312 (21 CFR part 312), sponsors must submit chemistry, manufacturing and control (CMC) information on a drug or biological product as part of an IND application (§ 312.23(a)(7)) (Refs. 1 through 6). FDA reviews the submitted IND to determine whether the phase 1 investigational drug to be used in the clinical trial is sufficiently safe to permit the trial to proceed. This determination is based, in part on whether the investigational product has the identity, strength, quality, and purity, and purported effect described in the IND application. In certain circumstances, FDA also may choose to conduct an inspection (e.g., if there is insufficient information to assess the risks to subjects or if the subjects would be exposed to unreasonable and significant risk). Finally, FDA could decide to place a proposed or ongoing phase 1 clinical trial on clinical hold or terminate the IND. FDA can also take any of these actions if there is evidence of inadequate QC procedures that would compromise the safety of an investigational product.

### **B. Guidance**

The 1991 guidance (reprinted in 1992) did not discuss all manufacturing situations, including, for example, small- or laboratory-scale manufacture of investigational products. In addition, the 1991 guidance did not address fully FDA's expectation for an appropriate approach to manufacturing controls during different phases of investigational product development, which for most products includes a change in manufacturing scale.

This guidance describes an approach manufacturers may use to implement manufacturing controls that are appropriate for the phase 1 clinical trial stage of development. The approach described in this guidance reflects the fact that some manufacturing controls and the extent of manufacturing controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical trials. Consistent with FDA's CGMP for the 21 Century initiative,<sup>4</sup> where applicable, manufacturers are also expected to implement manufacturing controls that reflect product and manufacturing considerations, evolving process and product knowledge, and manufacturing experience.<sup>5</sup>

The 1991 guidance will continue to be relevant for the manufacture of IND investigational drugs for use during phase 2 and 3 clinical trials (Ref. 1) and for the manufacture of non-exempt phase 1 investigational drugs. Phase 2 and 3 manufacturing will continue to be subject to parts 210 and 211.

### **III. SCOPE**

This guidance applies to investigational new drug and biological products (including finished dosage forms used as placebos) intended for human use during phase 1 development that are

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<sup>4</sup> See <http://www.fda.gov/cder/gmp/21stcenturysummary.htm>.

<sup>5</sup> We are considering issuing additional guidance and/or regulations to clarify FDA's expectations with regard to fulfilling the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical trials.

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subject to CGMP requirements of section 501(a)(2)(B) of the FD&C Act, and are excluded from complying with the CGMP regulations in 21 CFR part 211, by operation of 21 CFR 210.2(c). These include but are not limited to:

- Investigational recombinant and non-recombinant therapeutic products
- Vaccine products
- Allergenic products
- In vivo diagnostics
- Plasma derivative products
- Blood and blood components<sup>6</sup>
- Gene therapy products
- Somatic cellular therapy products (including xenotransplantation products).

This guidance applies to phase 1 investigational drugs whether they are manufactured in small- or large-scale environments because phase 1 clinical trials (21 CFR 312.21(a)) are typically designed to assess tolerability, or feasibility, for further development of a specific drug or biological product. Furthermore, if an investigational drug has already been manufactured by an IND sponsor for use during phase 2 or phase 3 clinical trials or has been lawfully marketed, manufacture of such a drug must comply (21 CFR 211.1) with 21 CFR part 211 for the drug to be used in any subsequent phase 1 clinical trials, irrespective of the trial size or duration of dosing. See 21 CFR 210.2(c).

This guidance does *not* apply to the following phase 1 investigational products:

- Human cell or tissue products regulated solely under § 361 of the Public Health Service Act
- Clinical trials for products subject to the device approval or clearance provisions of the FD&C Act
- Investigational products manufactured for phase 2 and phase 3 clinical trials<sup>7</sup>
- Already approved products that are being used during phase 1 clinical trials (e.g., for a new indication)<sup>6</sup>
- Positron Emission Topography (PET) drugs that are subject to § 501(a)(2)(C) of the FD&C Act and/or the new PET CGMP in 21 CFR part 212 when finalized

If you need clarification on the applicability of this guidance to a specific clinical trial, contact the appropriate FDA Center with responsibility for review of the IND.

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<sup>6</sup>We recommend you consult with the Office of Blood Research and Review, CBER, to determine circumstances when an IND would be required for blood or a blood component. Manufacturers of blood and blood components intended for transfusion and for further manufacture must still comply with the applicable regulations in 21 CFR parts 600 through 660.

<sup>7</sup> Manufacture of such a drug must comply with the appropriate sections of 21 CFR part 211 for the drug to be used in any subsequent phase 1 clinical trial, irrespective of the trial size or duration of dosing.

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This guidance is applicable to all manufacturers of phase 1 investigational drugs, including contractors and other specialized service providers as well as IND sponsors who participate in any aspect of manufacturing.

We (FDA) recommend that you use this guidance as a companion to other FDA guidance documents describing the chemistry, manufacturing, and control (CMC) information submitted and reviewed in an IND application for phase 1 clinical trials (Refs. 1 through 6). In many cases, at this stage of development manufacture of the active pharmaceutical ingredient and the phase 1 investigational drug will be accomplished through a series of steps within a single facility. Manufacturers of new active pharmaceutical ingredients (also referred to as *API* or *drug substance*) must also conform with CGMP as required in § 501(a)(2)(B) of the FD&C Act. Limited guidance is available on CGMP for the manufacture of new API in some IND products (Ref. 3). Manufacturers of APIs should implement CGMP appropriate to the stage of clinical development and consider the recommendations described in this guidance for the manufacture of APIs used in phase 1 investigational drugs.

#### **IV. GENERAL GUIDANCE FOR COMPLYING WITH THE STATUTE**

This guidance provides recommendations that manufacturers of phase 1 investigational drugs can use to comply with the statutory requirement for CGMP under § 501(a)(2)(B) of the FD&C Act. Manufacturers should also consult other resources, such as literature and technical bulletins for additional detailed information on CGMP that complement the approaches and recommendations in this guidance.

During product development, the quality and safety of phase 1 investigational drugs are maintained, in part, by having appropriate QC procedures in effect. Using established or standardized QC procedures and following appropriate CGMP will also facilitate the manufacture of equivalent or comparable IND product for future clinical trials as needed.

Adherence to CGMP during manufacture of phase 1 investigational drugs occurs mostly through:

- Well-defined, written procedures
- Adequately controlled equipment and manufacturing environment
- Accurately and consistently recorded data from manufacturing (including testing)

Manufacturers may have acceptable alternatives to meet the objectives described in this guidance. It is the manufacturer's responsibility to provide and use such methods, facilities, and manufacturing controls to ensure that the phase 1 investigational drug meets appropriate standards of safety, identity, strength, quality, and purity. Manufacturers of phase 1 investigational drugs should consider carefully how to best ensure the implementation of standards, practices, and procedures that conform to CGMP for their specific product and manufacturing operation.

In applying appropriate CGMP, we recommend that manufacturers consider carefully the hazards and associated risks from the manufacturing environment that might adversely affect the



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quality of a phase 1 investigational drug, especially when the phase 1 investigational drug is manufactured in laboratory facilities that are not expressly or solely designed for their manufacture. For example, of particular importance is the susceptibility of a phase 1 investigational drug to contamination or cross contamination with other substances (e.g. chemicals, biologicals, adventitious agents) that may be present from previous or concurrent research or manufacturing activities.

We recommend the following steps to establish the appropriate manufacturing environment for phase 1 investigational drugs:

- A comprehensive and systematic evaluation of the manufacturing setting (i.e., product environment, equipment, process, personnel, materials) to identify potential hazards
- Appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards to safeguard the quality of the phase 1 investigational drug

Any manufacturing environment, including a laboratory, should have adequate work areas that are properly equipped and controlled for the specific operation(s) needed to manufacture a phase 1 investigational drug. Given the diversity of products and requisite manufacturing operations, not all environments may be acceptable for the manufacture of the specific phase 1 investigational drug under consideration. In these situations, you should use more suitable facilities.

A number of technologies and resources are available that can facilitate conformance with CGMP and streamline product development. Some examples include:

- Use of disposable equipment and process aids to reduce cleaning burden and chances of contamination
- Use of commercial, prepackaged materials (e.g., Water For Injection (WFI), pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment
- Use of closed process equipment (i.e., the phase 1 investigational drug is not exposed to the environment during processing) to alleviate the need for stricter room classification for air quality
- Use of contract or shared CGMP manufacturing facilities and testing laboratories (including specialized services). For example, some academic institutions have developed shared manufacturing and testing facilities that can be used by institutional sponsors.

Under CGMP, if a sponsor or manufacturer initiates a contract with another party to perform part or all of the phase 1 investigational drug manufacturing, the sponsor or manufacturer, and contractor are both responsible for assuring that the phase 1 investigational drug is manufactured in compliance with CGMP. This assurance is achieved, in part, by having effective quality control functions (see section V.B). We recommend that the manufacturer or sponsor assess the contractor to ensure that effective quality control functions are in place.

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### **V. RECOMMENDED CGMP FOR PHASE 1 INVESTIGATIONAL DRUGS**

Consistent with the FD&C Act (§ 501(a) (2) (B)), CGMP must be in effect for the manufacture of each batch of investigational drug used during phase 1 clinical trials. Manufacturers should establish manufacturing controls based on identified hazards for the manufacturing setting that follow good scientific and QC principles. The following manufacturing controls are applicable to the manufacture of phase 1 investigational drugs and in some specific manufacturing situations. These recommendations provide flexibility to the manufacturers in implementing CGMP controls appropriate to their specific situation and application.

#### **A. Personnel**

All personnel should have the education, experience, and training or any combination thereof to enable each individual to perform their assigned function. In particular, personnel should have the appropriate experience to prepare the phase 1 investigational drug and be familiar with QC principles and acceptable methods for complying with the statutory requirement of CGMP, such as the recommendations described in this guidance.

#### **B. QC Function**

Every manufacturer should establish a written plan that describes the role of and responsibilities for QC functions.<sup>8</sup> For example, a written plan should provide, at a minimum, for the following functions.

- Responsibility for examining the various materials used in the manufacture of a phase 1 investigational drug (e.g., containers, closures, in-process materials, raw materials, packaging materials, and labeling) to ensure that they are appropriate and meet defined, relevant quality standards
- Responsibility for review and approval of manufacturing procedures, testing procedures, and acceptance criteria
- Responsibility for releasing or rejecting each batch of phase 1 investigational drug based on a cumulative review of completed manufacturing records and other relevant information (e.g., procedures were followed, product tests performed appropriately, acceptance criteria met)
- Responsibility for investigating unexpected results or errors that occur during manufacturing or from complaints received and initiation of corrective action, if appropriate.

Although quality is the responsibility of all personnel involved in manufacturing, we recommend that you assign an individual(s) to perform QC functions independent of manufacturing responsibilities, especially for the cumulative review and release of phase 1 investigational drug batches.

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<sup>8</sup> For some manufacturers, the Quality Control Function as described in this guidance may be assigned between a quality control and quality assurance group and may be integrated into a more comprehensive quality system.

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However, in very limited circumstances and depending on the size and structure of an organization, all QC functions may be performed by the same individual(s) performing manufacturing. For example, in some small operations, it may be necessary to have the same individual perform both manufacturing and QC functions, including release or rejection of each batch. However, in such circumstances, we strongly recommend that another qualified individual not involved in the manufacturing operation conduct an additional *periodic* review of manufacturing records and other QC activities.

When activities such as testing, commonly performed by dedicated QC personnel in commercial manufacture, are performed by manufacturing personnel in phase 1 studies, adequate controls should be in place (e.g., segregation of testing from manufacturing) so as to not contaminate testing or negatively affect test results.

### **C. Facility and Equipment**

Any facility used for manufacturing phase 1 investigational drugs should have adequate work areas and equipment for the intended task.

Each facility should provide the following described work area and equipment:

- Sufficient space, clean environment, appropriate construction
- Appropriate lighting, ventilation, and heating
- Appropriate cooling, plumbing, washing, and sanitation
- Appropriate equipment to maintain an air cleanliness classification suitable to the operation performed in the area. For example, appropriate air handling systems (e.g., laminar flow hoods) to aid in preventing contamination and cross-contamination of the phase 1 investigational drug.
- Appropriate equipment that will not contaminate the phase 1 investigational drug or otherwise react with, add to, or be absorbed by the phase 1 investigational drug; and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures.

We recommend that you identify all equipment used for a particular process and document such use in the manufacturing record. You should follow the provisions described under Sterile Products/Aseptically Processed Products (see section VI.C) for phase 1 investigational drugs prepared using aseptic processing.

Use of procedural controls in a facility promotes orderly manufacturing and aids in preventing contamination, cross contamination and mix-ups (see section VI.A).

### **D. Control of Components, and Containers and Closures**

You should establish written procedures describing the handling, review, acceptance, and control of material (i.e., components, containers, closures) used in the manufacture of a phase 1

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investigational drug. Materials should be controlled (e.g., segregated, labeled) until you have examined or tested the materials, as appropriate, and released them for use in manufacturing. It is important to handle and store such materials in a manner that prevents degradation or contamination.

The manufacturer should be able to identify and trace all materials used in the manufacture of a phase 1 investigational drug from receipt to use in the manufacture of each batch. We recommend that you keep a record (e.g., log book) containing relevant information on all materials. At a minimum, recorded relevant information would include receipt date, quantity of the shipment, supplier's name, material lot number, storage conditions, and corresponding expiration date.

The manufacturer should establish acceptance criteria for specified attributes on each material. For some materials, all relevant attributes or acceptance criteria may not be known at the phase 1 stage of product development. However, attributes and acceptance criteria selected for assessment should be based on scientific knowledge and experience for use in the specific phase 1 investigational drug. The material attributes and acceptance criteria will be reviewed in the IND application (Refs. 1 through 6).

We recommend that you examine the certificate of analysis (COA) and/or other documentation on each lot of material to ensure that it meets established acceptance criteria for specified attributes. For some (e.g., human and animal derived material), documentation should include information on sourcing and/or test results for adventitious agents, as appropriate. If documentation for a material is incomplete for a specified attribute, we recommend that you test for the incomplete specified attribute of the material. For each batch of the API (or drug substance), you should perform confirmatory identity testing.

#### **E. Manufacturing and Records**

The manufacture of phase 1 investigational drugs should follow written manufacturing and process control procedures that provide for the following records.

- A record of manufacturing data that details the materials, equipment, procedures used, and any problems encountered during manufacturing. We recommend that manufacturers retain records sufficient to replicate the manufacturing process. Similarly, if the manufacture of a phase 1 investigational drug batch is initiated but not completed, we recommend that the record include an explanation of why manufacturing was terminated.
- A record of changes in procedures and processes used for subsequent batches along with the rationale for any changes
- A record of the microbiological controls that have been implemented (including written procedures) for the production of sterile-processed phase 1 investigational drugs that are covered by this guidance. You should follow the recommendations for use of aseptic techniques and the control of in-process materials, components, and container closures designed to prevent microbial and endotoxin contamination (see section VI.C).

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### **F. Laboratory Controls**

#### *1. Testing*

Laboratory tests used in manufacturing (e.g., testing of materials, in-process material, packaging, drug product) should be scientifically sound (e.g., specific, sensitive, and accurate), suitable and reliable for the specified purpose. You should perform tests under controlled conditions and follow written procedures describing the testing methodology. You should maintain records of all test results, procedures, and changes in procedures.

You should perform laboratory testing of the phase 1 investigational drug to evaluate quality attributes including those that define the identity, strength, potency, purity, as appropriate. Specified attributes should be monitored, and acceptance criteria applied appropriately. For known safety-related concerns, specifications should be established and met. For some phase 1 investigational drug attributes, all relevant acceptance criteria may not be known at this stage of development. This information will be reviewed in the IND submission (Refs. 1 through 6).

To ensure reliability of test results, we recommend that you calibrate laboratory equipment at appropriate intervals and maintain the equipment according to established written procedures. We recommend that personnel verify that the equipment is in good working condition when samples are analyzed (e.g., system suitability).

You should retain a representative sample from each batch of phase 1 investigational drug. We recommend retention of both the API and phase 1 investigational drug in containers used in the clinical trials. When feasible, we recommend that the sample consist of a quantity adequate to perform additional testing or investigation if required at a later date (e.g., twice the quantity necessary to conduct release testing, excluding testing for pyrogenicity and sterility). We recommend that you appropriately store and retain the samples for at least two years following clinical trial termination, or withdrawal of the IND application.

#### *2. Stability*

We recommend initiation of a stability study using representative samples of the phase 1 investigational drug to monitor the stability and quality of the phase 1 investigational drug during the clinical trial (i.e., date of manufacture through date of last administration).<sup>9</sup>

### **G. Packaging, Labeling and Distributing**

The phase 1 investigational drug should be suitably packaged to protect it from alteration, contamination, and damage during storage, handling, and shipping. You should establish written procedures for controlling packaging, labeling, and distribution operations. We recommend the use of appropriate measures (e.g., product segregation, label reconciliation, verify operations by a second person, confirmatory laboratory testing, QC review) to achieve effective control

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<sup>9</sup> IND regulations require information sufficient to assure the drug product's stability during the planned studies (see 21CFR 312.23(a)(7)(iv) (b)).

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especially in situations where the potential for mix-ups is more likely (e.g., use of placebo, blinded trials, multiple strengths).

As it relates to phase 1 clinical trials, distribution includes the transport of a phase 1 investigational drug covered by this guidance to clinical investigators. You should handle phase 1 investigational drugs in accordance with labeled conditions (e.g., temperature) to ensure retention of the quality of the product. A distribution record of each batch of phase 1 investigational drug must be sufficiently detailed to allow traceability and facilitate recall of the phase 1 investigational drug if necessary (§ 312.57(a)).<sup>10</sup>

### **H. Recordkeeping**

As indicated in previous sections, manufacturers should keep complete records relating to the quality and operation of the manufacturing processes, including but not limited to:

- Equipment maintenance and calibration
- Manufacturing records and related analytical test records
- Distribution records
- QC functions (as defined in section V.B)
- Component records
- Deviations and investigations
- Complaints

Under § 312.57(c), sponsors must retain records for at least two years after a marketing application is approved for the drug, or if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued and FDA is notified.

## **VI. SPECIAL MANUFACTURING SITUATIONS**

### **A. Multi-Product Facilities**

We recommend that you manufacture only one phase 1 investigational drug at any given time, in an area or room separate from unrelated activities. However, you could use the same area or room for multiple purposes, including manufacture of other investigational products or laboratory research, provided that appropriate cleaning and procedural controls are in place to ensure that there is no carry-over of materials or products, or mix-ups. In such cases, the design or layout of an area should promote the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, previously manufactured products, personnel, or environmental conditions.

Examples of procedural controls could include procedures for clearing the room of previous product materials, product segregation, component segregation, and use of unique product

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<sup>10</sup> IND regulation 21 CFR 312.57 governs the retention of all records required by Part 312 (see 21 CFR 312.57).

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identifiers. We recommend that you periodically evaluate the implemented procedural controls for their effectiveness. You should take appropriate corrective action when indicated by the evaluation or when other events warrant.

### **B. Biological and Biotechnological Products**

#### *1. General Considerations*

The manufacturing process is critical to ensure the correct composition, quality, and safety of biological and biotechnology products. For these products, it can be difficult to distinguish changes in quality attributes, or predict the impact of observed changes in quality attributes on safety. This is especially true for phase 1 clinical trials where knowledge and understanding of a phase 1 investigational drug is limited and where comprehensive product characterization is often unavailable, especially for products that are difficult to characterize. Therefore, it is critical to carefully control and record the manufacturing process in conjunction with appropriate testing to reproduce a comparable phase 1 investigational drug as may be necessary. Properly stored retained samples (e.g., API or drug substance, in-process material, phase 1 investigational drug) that can be subsequently analyzed for comparison, can provide important links in reproducing comparable biological and biotechnological products.

You should have in place appropriate equipment and controls in manufacturing to ensure that unit operations with safety-related functions (e.g., viral clearance, virus/toxin attenuation, pasteurization) perform their function with a high degree of assurance. Specific testing may also serve to complement these functions. In manufacturing, you should use testing for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, virus clearance (i.e., removal or inactivation), and removal of residual substances (e.g., antibiotics, chemicals) as appropriate (see section VI.B.2).

#### *2. Adventitious Agent Control*

When evaluating the manufacturing environment for biological and biotechnology phase 1 investigational drugs, it is of particular importance to evaluate for susceptibility to contaminate the environment with biological substances, including microbial adventitious agents (e.g., bacterial, viral, mycoplasma), that may remain from previous research or manufacturing activities.

Some biological and biotechnology phase 1 investigational drugs, including those made from pathogenic microorganisms, spore-forming microorganisms, transgenic animals and plants, live viral vaccines, and gene therapy vectors, warrant additional containment considerations. We encourage you to discuss such containment issues with the applicable Center within FDA (i.e., product and facility group with responsibility for the product) prior to engaging in manufacturing.

In addition to the recommendation in section VI.A, multi-product facilities should have in place cleaning and testing procedures that ensure prevention and/or detection of contamination by adventitious agents. To the extent possible, we recommend the use of dedicated equipment

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and/or disposable parts (e.g., tubing) for this reason. For multi-product areas, you should establish procedures to prevent cross-contamination, and to demonstrate removal of the previously manufactured product from shared equipment and work surfaces, especially if live viral and vector processing occurs in a manufacturing area.

### ***3. Gene Therapy and Cellular Therapy Products***

Due to the wide variety and unique manufacturing aspects of investigational gene and cellular therapy products, manufacturers should consider the appropriateness of additional or specialized controls. Although you should manufacture phase 1 investigational cell and gene therapy products following the recommendations in this guidance, we recognize that it may not be possible to follow each recommendation. For example, with some cellular products, it may be impossible to retain samples of the final cellular product due to the limited amounts of material available. Therefore, we recommend that you include your justification for adopting additional controls or alternative approaches to the recommendations in this guidance in the records on the phase 1 investigational drug.

In some cases, investigational gene and cellular therapy products may be manufactured as one batch per subject in phase 1 clinical trials (e.g., gene vector modified autologous cell products, autologous cell products). Manufacture of multiple batches will allow manufacturing and testing information to accumulate in an accelerated manner as compared to more conventional products. As manufacturing methods and assays used for testing can be novel for these products, it is important to monitor manufacturing performance to ensure product safety and quality.

When manufacturing multiple batches of the same phase 1 investigational drug, we recommend that manufacturers periodically conduct and document internal performance reviews. We recommend that this review assess whether the manufacturing process is optimal to ensure overall product quality. Based on the review, appropriate modifications and corrective actions can be taken to control procedures and manufacturing operations.

### **C. Sterile Products/Aseptically Processed Products**

Because product sterility is a critical element of human subject safety, you should take special precautions for phase 1 investigational drugs that are intended to be sterile. You should give thorough consideration to implementing appropriate controls for aseptic processing to ensure a sterile phase 1 investigational drug. The guidance issued by FDA on aseptic processing is a good reference when using aseptic processing (Ref. 7). Particular manufacturing controls include:

- Conducting aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, biosafety cabinets, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5. You should perform all manipulations of sterile products and materials under aseptic conditions.
- Conducting a process simulation using bacterial growth media to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile drug



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- Performing environmental monitoring of the aseptic workstation during processing to ensure appropriate microbiological control. Such monitoring may include microbial monitoring by settling plates or by active air monitoring.
- Disinfecting the entire aseptic workstation as appropriate to the nature of the operations (e.g., before aseptic manipulation, or between different operations during the same day)
- Ensuring proper workstation installation and placement (e.g., workstations sufficiently separated to allow appropriate airflow) and ensuring that items within a laminar airflow aseptic workstation do not interrupt the unidirectional airflow
- Disinfecting gloves or changing them frequently when working in the laminar flow hood
- Disinfecting the surface of nonsterile items (e.g., test tube rack, and the overwrap for sterile syringes and filters) with sterile disinfectant solution before placing them in the laminar flow hood
- Documenting and following all procedures intended to maintain the sterility of the components, in-process materials, and final phase 1 investigational drug
- Demonstrating that the test article does not interfere with the sterility tests (e.g., USP <71>)
- Employing aseptic technique and control of microbiological impurities in components designed to prevent microbial and endotoxin contamination
- Training personnel in using aseptic techniques
- Verifying that the equipment is suitable for its intended use, i.e., sterilization (e.g., autoclave, hot air oven); performing appropriate calibration of temperature probes used to monitor the sterilization cycle; using suitable and qualified biological indicators; and retaining maintenance and cycle run log records
- Demonstrating that the sterilization method for sterile components and disposable equipment (e.g., filters, bags, containers/ stoppers) is suitable and creating documentation that supports the appropriate use and shelf life of sterile components and equipment
- Ensuring that release of the final phase 1 investigational drug by the QC unit, or designated individual, includes an acceptable review of manufacturing records that demonstrate aseptic procedures and precautions were followed
- Ensuring that final phase 1 investigational drugs are not released until acceptable results of sterility testing are known. We understand that you may have to release a phase 1 investigational drug with a short shelf-life (e.g., radiopharmaceutical, cellular product) based on results from relevant tests (e.g., assessment of sterile filtration by bubble point filter integrity test, cell product — an in-process test result and a negative gram stain, or other rapid microbial detection test and negative endotoxin test on the final product) while results of the sterility test are pending. When you obtain positive results or other relevant results from sterility testing, we recommend that you perform an investigation to

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determine the cause of contamination followed by corrective action, if warranted. You should notify the person responsible for the associated clinical trials so appropriate action can be taken.

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### **GLOSSARY**

**Acceptance Criteria** means numerical limits, ranges, or other suitable measures of test results necessary to determine acceptance of the drug substance, drug products, or materials at stages of their manufacture.

**Active Pharmaceutical Ingredient (API) (or drug substance)** means any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

**Batch** means a specific quantity of a drug or other material intended to have uniform character and quality, within specified limits, and is manufactured according to a single manufacturing order during the same cycle of manufacture.

**Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

**Contamination** means the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, in-process material, or phase 1 investigational drug during manufacturing, sampling, packaging or repackaging, storage, or transport.

**Cross-Contamination** means contamination of a material or phase 1 investigational drug with another material or product.

**Drug product** means a finished dosage form (e.g., tablet, capsule, solution) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient, but is intended to be used as a placebo.

**In-process material** means any material fabricated, compounded, blended, or derived by chemical reaction (e.g., intermediate) that is manufactured for, and used in, the preparation of the phase 1 investigational drug.

**Phase 1 investigational drug** – a new drug or biological drug that is used in phase 1 of a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes.

**Multiproduct** means more than one approved product, licensed product, IND drug; or separate process.

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**Manufacture** (production) means all operations involved in the preparation of a phase 1 investigational drug from receipt of materials through distribution including processing, storage, packaging, labeling, laboratory testing, and QC.

**Manufacturer** means a person who takes responsibility for and is involved in any aspect of the manufacture of a phase 1 investigational drug.

**Procedural control** means manufacturing methodologies executed in such a manner as to prevent or minimize contamination.

**Specification** means a list of tests, references to analytical procedures, and appropriate acceptance criteria or other criteria for the tests. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

**Sponsor** means a person who takes responsibility for and initiates a clinical investigation.

## **REFERENCES**

1. FDA guidance on the “Preparation of Investigational New Drug Products (Human and Animal)” 1991 (reprinted November 1992).
2. FDA “Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies.”
3. FDA “Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,” Section 19.
4. FDA “Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.”
5. FDA “Draft Guidance for Industry: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs),” August 2003.
6. FDA “Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs),” November 2004.
7. FDA “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices.”