the Qualified Person may then certify on the basis of documentation supplied by the 3rd country manufacturer (see 40).

c) For imported comparator products where adequate assurance cannot be obtained in order to certify that each batch has been manufactured to equivalent standards of Good Manufacturing Practice, the duty of the Qualified Person is defined in article 13.3(c) of Directive 2001/20/EC.

40. Assessment of each batch for certification prior to release may include as appropriate:

batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;

production conditions;

the validation status of facilities, processes and methods;

examination of finished packs;

where relevant, the results of any analyses or tests performed after importation;

stability reports;

the source and verification of conditions of storage and shipment;

audit reports concerning the quality system of the manufacturer;

Documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;

where relevant, regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance;

all other factors of which the QP is aware that are relevant to the quality of the batch.

The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorisation, in the EU or in a third country) and its phase of development.

The sponsor should ensure that the elements taken into account by the qualified person when certifying the batch are consistent with the information notified pursuant to Article 9(2) of Directive 2001/20/EC. See also 44.

41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Qualified Persons, the recommendations listed in Annex 16 to the GMP Guide should be followed as applicable.

42. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Qualified Person in this regard.

SHIPPING

43. Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

44. Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step release procedure: certification by the Qualified Person; and release following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. The sponsor should ensure that these are consistent with the details actually considered by the Qualified Person. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

45. De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.

46. A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.

47. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Qualified person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer for re-labelling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

COMPLAINTS

48. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the Qualified Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

RECALLS AND RETURNS

Recalls

49. Procedures for retrieving investigational medicinal products and documenting this

retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.

50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

Returns

51. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

52. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

DESTRUCTION

53. The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor.

54. The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

55. When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

TABLE 1. SUMMARY OF LABELLING DETAILS (§26 to 30)

a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

(c) the batch and/or code number to identify the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the trial subject identification number/treatment number and where relevant, the visit number;

(f) the name of the investigator (if not included in (a) or (d);

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

(h) "for clinical trial use only" or similar wording;

(i) the storage conditions;

(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

(k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

GENERAL CASE
For both the outer packaging and immediate container (§26)

Particulars
a[1] to k

IMMEDIATE CONTAINER
Where immediate container and outer packaging remain together throughout (§29)[5]

a[2] b[3] c d e

IMMEDIATE CONTAINER
Blisters or small packaging units (§30)[5]

a[2] b[3,4] c d e

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[1] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).

[2] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

[3] Route of administration may be excluded for oral solid dose forms.

[4] The pharmaceutical dosage form and quantity of dosage units may be omitted.

[5] When the outer packaging carries the particulars listed in Article 26.

Table 2: BATCH RELEASE OF PRODUCTS

ELEMENTS TO BE TAKEN INTO ACCOUNT[3]	PRODUCT AVAILABLE IN THE EU		PRODUCT IMPORTED FROM THIRD COUNTRIES		
	Product manufactured in EU without MA	Product with MA and available on EU market	Product without any EU MA	Product with a EU MA	Comparator where documentation certifying that each batch has been manufactured in conditions at least equivalent to those laid down in Directive 91/356/EEC cannot be obtained
BEFORE CLINICAL TRIAL PROCESSING					
a) Shipping and storage conditions	Yes				
b) All relevant factors (1) showing that each batch has been manufactured and released in accordance with: Directive 91/356/EEC, or GMP standards at least equivalent to those laid down in Directive 91/356/EEC.	Yes -		(2) yes		
c) Documentation showing that each batch has been released within the EU according to EU GMP requirements (see Directive 2001/83/EC, article 51), or documentation showing that the product is available on the EU market and has been procured in accordance with article 80(b) of Directive 2001/83/EC.		Yes			
d) Documentation showing that the product is available on the local market and documentation to establish confidence in the local regulatory requirements for marketing authorisation and release for local use.					Yes
e) Results of all analysis, tests and checks performed to assess the quality of the imported batch according to: the requirements of the MA (see Directive 2001/83/EC, article 51b), or the Product Specification File, the Order, article 9.2 submission to the regulatory authorities. Where these analyses and tests are not performed in the EU, this should be justified and the QP must certify that they have been carried out in accordance with GMP standards at least equivalent to those laid down in Directive 91/356/EEC.			- yes yes	yes - yes	- yes yes
AFTER CLINICAL TRIAL PROCESSING					
f) In addition to the assessment before clinical trial processing, all further relevant factors (1) showing that each batch has been processed for the purposes of blinding, trial-specific packaging, labelling and testing in accordance with: Directive 91/356/EEC, or GMP standards at least equivalent to those laid down in Directive 91/356/EEC.	Yes -		(2) yes		

(1) These factors are summarised in paragraph 40.

(2) Where an MRA or similar arrangements are in place covering the products in question, equivalent standards of GMP apply.

(3) In all cases the information notified pursuant to Article 9(2) of Directive 2001/20/EC should be consistent with the elements actually taken into account by the QP who certifies the batch prior to release

Guidance for Industry

INDs — Approaches to Complying with CGMP During Phase 1

Draft Guidance

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Monica Caphart at 301-827-9047 or (CBER) Christopher Joneckis at 301-435-5681.

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)

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CGMP

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Guidance for Industry

INDs — Approaches to Complying with CGMP During Phase 1

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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)

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1/9/2006

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry
INDs — Approaches to Complying with CGMP During Phase 1[1]

This draft guidance, when finalized, will represent 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 persons producing drug and biological products (investigational drugs) for use during phase 1 development (21 CFR 312.21(a)) in complying with relevant current good manufacturing practice as required by § 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Controls for producing an investigational new drug for use in a phase 1 study are primarily aimed at ensuring subject safety. The Agency believes that applying quality control (QC) principles to the production of investigational products (i.e., interpreting and implementing CGMPs consistent with good scientific methodology) will facilitate the initiation of investigational studies in humans and protect study subjects. When finalized, this guidance will replace the *1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal)* for the production of IND products for phase 1 clinical trials described in the Scope section of this guidance.

This guidance is being issued concurrently with a direct final rule (and companion proposed rule), which specifies that the particular requirements in Part 211 (21 CFR 211) need not be met for most investigational drugs manufactured for use during phase 1 development. Instead, the Agency recommends 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.

[1] 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 Adminstration.

II. BACKGROUND

The FD&C Act specifies that drugs must be manufactured, processed, packed, and held in accordance with current good manufacturing practice (CGMP), or they are deemed to be adulterated. In September 1978, FDA implemented revised CGMP regulations for drug and biological products (see 21 CFR Parts 210 and 211). These regulations were written primarily with commercial manufacturing in mind. Although the Agency stated at the time that the regulations applied to all types of pharmaceutical production,[2] we indicated in the preamble to the regulations that we were considering proposing additional regulations governing drugs used in investigational clinical studies.

In 1991, the Agency issued the *Guideline on the Preparation of Investigational New Drug Products (Human and Animal).* However, the 1991 document did not discuss all manufacturing situations, including, for example, small- or laboratory-scale production of investigational new drugs. In addition, the 1991 document did not address fully the Agency's expectation that an ***incremental approach*** to manufacturing controls would be taken during investigational drug development, which for most products includes a change in production scale.

This guidance (once finalized) and the regulation it complements, once finalized, will represent the Agency's effort to proceed with its plans to formally describe an approach to aide manufacturers in implementing manufacturing controls that are appropriate for the stage of development. The use of this approach recognizes that some controls and the extent of controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical studies. Consistent with the Agency's CGMP for the 21 Century initiative,[3] where applicable, manufacturers are also expected to implement controls that reflect product and production considerations, evolving process and product knowledge, and manufacturing experience.[4]

This guidance describes FDA's current thinking regarding controls for special production situations (e.g., a laboratory setting, exploratory studies, multi-product and multi-batch testing) and specific types (e.g., biological/biotechnology products, aseptically processed products) of investigational new drug (IND) products manufactured for use during phase 1 clinical trials as described in the Scope section of this guidance. As the new rule specifies, the particular requirements in Parts 211 (21 CFR 211) need not be met for certain exploratory products manufactured for use during phase 1 clinical trials.

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[2] 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."

[3] See http://www.fda.gov/cder/gmp/21stcenturysummary.htm.

[4] We are considering issuing additional guidance and/or regulations to clarify the Agency's expectations with regard to fulfilling the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies.

When finalized, this guidance will replace the *1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal)* for the production of IND products for phase 1 clinical trials described in the Scope section of this guidance. Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable.

III. SCOPE

This guidance applies to the following:

> Investigational new human drug and biological products (including finished dosage forms used as placebos) intended for human use during phase 1 development, including, for example, investigational recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood components, gene therapy products, and somatic cellular therapy products (including xenotransplantation products) that are subject to CGMP requirements of § 501(a)(2)(B) of the FD&C Act.

The guidance applies to investigational products whether they are produced in small- or large-scale environments because such studies are typically designed to assess tolerability or feasibility for further development of a specific drug or biological product. However, if an investigational drug has already been manufactured by an IND sponsor for use during phase 2 or phase 3 studies or has been lawfully marketed, 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 investigational studies, irrespective of the trial size or duration of dosing.

This guidance does ***not*** apply to the following:

- Human cell or tissue products regulated solely under Section 361 of the PHS Act
- Clinical trials for products subject to the device approval or clearance provisions of the Food, Drug, and cosmetic Act
- Investigational new drugs manufactured for phase 2 and 3 studies
- Already approved products that are being used during phase 1 studies (e.g., for a new indication)

If clarification on applicability of this guidance to a specific clinical study is needed, please contact the appropriate center with responsibility for review of the IND.

We recommend that this guidance be used as a companion to other guidances describing the chemistry, manufacturing, and control (CMC) information submitted and reviewed in an IND application for phase 1 studies (References 1, 2, 3). At this stage of development, in many cases, manufacture of the active ingredient and the final investigational product will be accomplished through a series of steps within a single facility. Producers of new active pharmaceutical

ingredients (also referred to as an *API* or *drug substance*) must also conform with CGMP as required in § 501(a)(2)(B) of the FD&C Act. Guidance on CGMP for the manufacture of new API for some products used in clinical studies is also available (Reference 4). Such producers should implement controls appropriate to the stage of development and, thus, may want to consider the recommendations described in this guidance.

IV. STATUTORY AND REGULATORY REQUIREMENTS

Section 501(a)(2)(B) of the FD&C Act requires drugs, which include investigational new drugs, to comply with current good manufacturing practice:

> 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 chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess

Certain of the requirements of 21 CFR Parts 211, which implement section § 501(a)(2)(B) of the FD&C Act, were directed at commercial manufacture of products, typically characterized by large, repetitive, commercial batch production (e.g., those that address expiration dating (§ 211.137(g)), and warehousing (§ 211.142) and are not relevant to the manufacture of most drugs for investigational use for phase 1 studies.

In addition, section 505(i) of the FD&C Act (21 U.S.C. 355(i)) directs FDA to promulgate regulations governing investigational drugs to protect human subjects enrolled in investigations. Under these regulations (21 CFR 312), sponsors must submit information — for example CMC information (§ 312.23(a)(7)) — about a drug or biological product when submitting an IND application (References 1, 2, 3). FDA reviews the submitted information to determine whether the drug to be used in the investigation has the identity, quality, purity, strength, and potency necessary to ensure the safety of the subjects in the proposed phase 1 study. In certain circumstances, the Agency 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). Alternatively, the Agency could decide to place a proposed or ongoing phase 1 investigation on clinical hold or terminate the IND. Such actions can also be taken if there is evidence of inadequate quality control procedures that would compromise the safety of an investigational product.

V. RECOMMENDATIONS FOR COMPLYING WITH THE STATUTE

This guidance outlines approaches that sponsors and producers of phase 1 investigational new drugs can use to comply with the requirements of CGMP under section 501(a)(2)(B) of the FD&C Act. These recommendations are designed to provide approaches to CGMP that appropriately address factors associated with the production of clinical supplies for use in most

phase 1 studies. The recommendations will also help provide an appropriate quality framework for a variety of investigational new drugs manufactured in various situations.

During product development, the quality and safety of investigational drug products are maintained, in part, by having appropriate quality control (QC) procedures in effect. Using established or standardized procedures will also facilitate the production of equivalent or comparable investigational product for further clinical study as needed.

Adherence to QC procedures during phase 1 development occurs largely through having:

- Written procedures that are well defined
- Equipment that is adequately controlled
- Data from production, including testing, that are accurately and consistently recorded

Producers may have acceptable alternative ways of meeting the objectives described in this guidance. It is the responsibility of the sponsors/producers to provide and use such methods, facilities, and controls to ensure that the investigational drug meets appropriate standards of safety, identity, strength, quality, and purity. Producers of investigational products should consider carefully how to best ensure the implementation of standards, practices and procedures that conform to CGMP for their specific product and production operation.

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

- Use of disposable equipment and process aids, which can reduce cleaning burden
- Use of prepackaged Water For Injection (WFI) and presterilized containers, which can eliminate the need for additional equipment or qualifying existing equipment
- Use of process equipment that is closed (i.e., product not exposed to the environment during processing), which can alleviate the need for stricter room classification for air quality
- Use of contract or shared production facilities and testing laboratories, for production and testing (including specialized services) of investigational product. Some academic institutions have developed shared production and testing facilities that can be used by institutional sponsors.

Because the sponsor is responsible for important aspects of the clinical investigation, we recommend that sponsors and producers consider carefully the risks from the production environment that might adversely affect the resulting quality of an investigational product, especially when the investigational product is produced in laboratory facilities that are not expressly or solely designed for their production. For example, of particular importance is the susceptibility of a product to contamination or cross contamination with other substances (e.g. chemicals, biological substances, adventitious agents) that may be present from previous or concurrent research or production activities.

We recommend the following:

- A formal evaluation of the production environment to identify potential hazards
- Taking of appropriate actions prior to and during production to minimize risks and safeguard the quality of the investigational product

Some recommendations pertaining to specific areas of CGMP follow. Consistent with the statute (§ 501(a) (2) (b)), CGMP must be in effect for the production of each investigational drug batch used in clinical trials. The following recommendations provide for flexibility to allow producers to implement controls appropriate for their specific situation and application. Producers should establish production controls based on a risk assessment for the product and manufacturing process and follow good scientific and quality control principles when implementing specific practices and procedures for CGMP.

A. Personnel

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

B. Quality Control Function

We recommend that every producer establish a QC plan and document that plan in writing. For example, a sound QC plan should provide for the following functions:

- Responsibility for examining the various components used in the production of a product (e.g., containers, closures, in-process materials, packaging materials, and labeling) to ensure that they are appropriate and meet defined, relevant quality standards
- Responsibility for review and approval of production procedures, testing procedures, and acceptance criteria
- Responsibility for releasing or rejecting each clinical batch based upon a cumulative review of completed production records and other relevant information (e.g., procedures were followed, product tests performed appropriately, acceptance criteria met)
- Responsibility for investigating and initiating corrective action if unexpected results or errors occur during production

We also recommend that QC responsibilities be performed independently from production responsibilities. When activities such as testing, commonly performed by dedicated QC personnel in commercial manufacture, are performed by production personnel, adequate controls should be in place (e.g., segregation of testing from production so as to not contaminate testing or negatively affect test results).

However, in limited circumstances, depending on the size and structure of an organization, all QC functions could be performed by the same individual. For example, in some small operations, it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch. Under such circumstances, we recommend that another qualified individual not involved in the production operation carry out an additional, periodic review of production records. It is important to note that quality should be the responsibility of all personnel involved in manufacturing

C. Facility and Equipment

Any facility, including a laboratory, used for production of investigational drugs for use in phase 1 studies should have adequate work areas and equipment for the intended task:

- Sufficient space, clean environment, appropriate construction
- Appropriate lighting, ventilation, and heating
- Appropriate cooling, plumbing, washing, and sanitation
- Appropriate air handling systems (e.g., laminar flow hoods) to aid in preventing contamination and cross-contamination of product
- Appropriate equipment that will not contaminate the product or otherwise be reactive, additive, or absorptive with the product and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures

We recommend that all equipment used for a particular process be identified and documented in the production record. We also recommend that the provisions in section VI.D, Sterile Products/Aseptically Processed Products, be followed for investigational products prepared using aseptic processing.

Use of procedural controls in an appropriate facility promotes orderly production and aids in preventing contamination, cross contamination and mix-ups (see Section VI.B).

D. Control of Components

We recommend there be written procedures describing the handling, review, and acceptance and control of components used in the production of an investigational product. Components should be controlled (e.g., segregated, labeled) until they have been examined or tested, as appropriate, and released for use in production. It is important to handle and store components in a manner that prevents degradation or contamination. We recommend keeping a record (e.g., log book) containing relevant information on all components. Information to record would include receipt date, quantity of the shipment, supplier's name, component lot number, investigational product batch number, storage conditions, and corresponding expiration date.

We recommend establishing acceptance criteria for specified attributes on each component. For some components, all relevant attributes or acceptance criteria may not be known at this 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 investigational

drug. The component attributes and acceptance criteria will be reviewed in the IND application (Ref 1-3).

We recommend that the certificate of analysis (COA) and/or other documentation on each lot of component be examined to ensure that it meets established acceptance criteria for specified attributes. For some materials (e.g., human and animal derived), documentation should include information on sourcing and/or test results for adventitious agents, as appropriate. If documentation for a component is incomplete, testing for the incomplete attribute of the component is recommended. For each batch of the drug substance (or API), we strongly recommend performing confirmatory identity testing, regardless of whether documentation has been provided.

E. Production and Documentation

We recommend that production of investigational products follow written production procedures that provide the following:

- A record of laboratory testing and production data that details the components, equipment, and procedures used. We recommend that sponsors retain documentation sufficient to replicate the production process. Similarly, if production of a clinical batch is initiated but not completed, we recommend that the record include an explanation of why production 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 investigational new drugs that are covered by this guidance. We also recommend the use of aseptic techniques and the control of in-process components designed to prevent microbial and endotoxin contamination (see Section VI.D, Sterile Products/Aseptically Processed Products).

F. Laboratory Controls

1. Testing

Analytical tests used in production (e.g., testing of components, in-process material, packaging, drug product) should be scientifically sound (e.g., specific, sensitive, and accurate) and reproducible for the specified purpose. We recommend that tests be performed under controlled conditions and follow written procedures describing the testing methodology.

Laboratory testing of the investigational product to evaluate identity, strength, potency, purity, and quality attributes should be performed, 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 product attributes, all relevant acceptance criteria may not be known at this stage of product development. This information will be reviewed in the IND submission (References 1, 2, 3).

We recommend that laboratory equipment be calibrated at appropriate intervals and be maintained according to established written procedures to ensure reliability of test results. We recommend that personnel verify that the equipment is in good working condition when samples are analyzed (e.g., systems suitability).

We further recommend that a representative sample from each product batch be retained. When feasible, we recommend that the sample consist of twice the quantity necessary to conduct release testing (excluding any testing for pyrogenicity and sterility). We recommend that the samples be appropriately stored and retained for at least 2 years following study termination, or withdrawal of the IND application.

2. Stability

We recommend that sponsors initiate a stability study using representative samples of the investigational new drug to monitor the stability and quality of the product during the clinical investigation (i.e., date of manufacture through date of last administration).

G. Container Closure and Labeling

When an investigational new drug covered by this guidance will be stored or shipped, the product should be suitably packaged to protect it from alteration, contamination, and damage during conditions of storage, handling, and shipping. We recommend that labeling and storage operations be controlled to prevent the possibility of mix-ups.

H. Distribution

As it relates to phase 1 trials, the term *distribution* includes the transport of an investigational new product covered by this guidance to clinical investigators and, ultimately, to the subjects enrolled in the study. Products should be handled in accordance with labeled conditions (e.g., temperature) to ensure retention of the quality of the product. A distribution record of each batch of investigational new drug covered by this guidance must be sufficiently detailed to allow traceability and facilitate recall of the product if necessary (§ 312.57).[5]

I. Recordkeeping

As indicated in previous sections, we recommend that sponsors keep complete records relating to the quality and operation of the production processes, including:

- Equipment maintenance and calibration
- Production records and related analytical test records
- Distribution records
- All quality control functions
- Component records

[5] IND regulation 21 CFR 312.57 governs the retention of all records required by Part 312 (see 21 CFR 312.57(C)).

Under the applicable IND regulations, sponsors must retain records for at least 2 years after a marketing application is approved for the drug, or if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA is notified.[6]

VI. SPECIAL PRODUCTION SITUATIONS

A. Screening Studies/Microdose Producers

A *screening study*, which is performed under an exploratory IND application, is intended to compare the properties of related active moieties to screen for the preferred compound or formulations for additional clinical development under a traditional IND application (Reference 5). Screening studies involve single-dose or short-term (e.g., ≤7 days of dosing) studies in humans of up to 5 chemically or pharmacologically related new chemical entities.

Microdose studies are defined as studies in which participants are administered a single dose of less than $1/100^{th}$ of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained in vitro and in vivo (typically doses in, or below the low microgram range) and at a maximum dose of ≤ 100 micrograms.

These types of investigational studies are often performed in small-scale laboratories or research organizations.[7] In such cases, special considerations are warranted. For example, when the same area or room is used for both the production of investigational products and research, we recommend that the sponsor segregate the operations sufficiently to

- Promote the orderly handling of materials and equipment
- Avoid contamination of equipment and product by other substances, personnel, or environmental conditions
- Prevent mix-ups

Reagents and components used for investigational product production may be stored safely in the same area as those used for research as long as they are properly labeled and organized in a manner that avoids mix-ups or unintended use.

Finally, we recommend that equipment be used for a single purpose (i.e., research only or production only) at any given time.

B. Multi-Product Facilities

[6] Ibid.

[7] A draft guidance entitled *Exploratory IND Studies* issued in April 2005. The guidance clarifies what preclinical and clinical issues (including chemistry, manufacturing, and controls issues) should be considered when planning exploratory studies. Once finalized, it will represent the Agency's thinking on this topic.

Ideally, we recommend that one product be produced in an area or room at any given time separate from unrelated activities. However, the same area or room could be used for multiple purposes, including production of other investigational products or laboratory research, provided that appropriate cleaning and control procedures are in place to ensure that there is no carry-over of materials or products or mix-ups. We recommend that in such cases, the design or layout of an area 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 produced products, personnel, or environmental conditions.

Additional controls could include procedures for clearing the room of previous product materials, product segregation, component segregation, and use of unique identifiers. We recommend that the implemented controls be assessed periodically to evaluate their effectiveness. Appropriate corrective action should be taken as a result of this assessment, or when other events warrant.

C. Biological and Biotechnological Products

1. General Considerations

Some biological and biotechnology investigational products, 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 early discussions with the applicable Agency center (i.e., product and facility group with responsibility for the product) prior to engaging in the production of such IND products.

The production process is critical to ensuring the correct composition 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 studies where knowledge and understanding of an investigational new drug is limited and where comprehensive product characterization is often unavailable, especially for products that are difficult to characterize. Therefore, it is critical, beginning with phase 1 studies, to adequately control and document the production process in conjunction with appropriate testing to reproduce comparable IND product as necessary. Retained samples (e.g., drug substance, drug product, intermediate, in-process material) that can be subsequently analyzed for comparison, can provide important links in reproducing comparable biological and biotechnological products.

We recommend that appropriate equipment qualification and controls in production be in place to ensure that units with safety-related functions (e.g., viral clearance, virus/toxin attenuation, pasteurization) will perform as intended. Specific testing may also serve to complement these functions. We recommend that testing for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, virus clearance or inactivation, and clearance of substances (e.g., antibiotics, chemicals) be used in production and that adventitious agent testing be established as appropriate.

Of particular importance in evaluating the environment to be used for production (see section V) is the susceptibility of biotechnology and biological products to contamination with biological substances including microbial adventitious agents (e.g., bacterial, viral, mycoplasm) that may remain from previous research or production activities.

2. Multi-Product Facilities

In addition to the recommendation in section VI.B, we recommend that multi-product facilities have cleaning and testing procedures in place that ensure prevention and/or detection of contamination by adventitious agents. To the extent possible, dedicated equipment and/or disposable parts (e.g., tubing) is recommended. For multi-product areas, we recommend that procedures be established to prevent cross-contamination and that demonstrate removal of the previously manufactured product from shared equipment and work surfaces, especially if live viral and vector processing occurs in a production area.

3. Gene Therapy and Cellular Therapy Products

Due to the wide variety and unique production aspects of investigational gene and cellular therapy products, producers should consider the appropriateness of additional or specialized controls. Although we recommend that investigational cell and gene therapy products be produced 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. We recommend that reasons for adopted approaches be included in the records on the investigational product.

4. Multi-Batch Producers

We are aware that, in some cases, investigational biological and biotechnology products covered by this guidance may be produced as frequently as one batch per subject in phase 1 studies (e.g., therapeutic vaccines, cell therapies, gene therapies). Production of multiple batches will allow additional production and testing information to accumulate in an accelerated manner as compared to more conventional products. It is also important to have and adhere to appropriate control procedures that enable the consistent manufacture of comparable drug substance and drug products.

When producing multiple batches of the same investigational product, we recommend that producers periodically conduct and document internal performance reviews. We recommend that such a review assess the control and consistency of the production process and overall product quality. This review would fall outside of routine production operations and would be conducted to assess procedures, practices, and information, including data generated from production and investigational new drug testing. Based on the review, appropriate modifications and corrective actions can be taken to control procedures and production operations. The data generated with each batch can also allow the producer to establish and/or refine acceptance criteria as experience and knowledge permits and, therefore, to achieve more consistent investigational new drug production.