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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

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PUBLIC HEALTH SERVICE
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GUIDELINE ON THE PREPARATION OF INVESTIGATIONAL NEW DRUG PRODUCTS (HUMAN AND ANIMAL)

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GUIDELINE ON THE PREPARATION OF INVESTIGATIONAL NEW DRUG PRODUCTS

(HUMAN AND ANIMAL)

I. PURPOSE

This guideline informs interested persons on certain practices and procedures for the preparation of investigational new drug products for human and animal use that may be useful to persons seeking to comply with certain sections of the current good manufacturing practice (CGMP) regulations for finished pharmaceuticals (Title 21 of the Code of Federal Regulations, Parts 210 and 211).

II. INTRODUCTION

The notice of availability of the draft guideline (53 FR 5835) stated that this guideline would be issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to establish procedures or standards of general applicability that are not legal requirements but that are acceptable to the agency. The agency is now in the process of considering whether to revise § 10.90(b). Although that decision-making process is not yet complete, the agency has decided to publish this guideline. However, this final guideline is not being issued under the authority of § 10.90(b), and, although called a guideline, it does not operate to bind the FDA or any other person in any way.

The agency advises that this final guideline represents its current position on the requirements of the CGMP regulations. The guideline may be useful to manufacturers of investigational new drug products produced for clinical trials in humans and animals. A person may also choose to use alternate procedures even though they are not provided for in the guideline. If a person chooses to depart from the practices and procedures set forth in the final guideline, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable by FDA. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

This guideline may be amended from time to time as FDA recognizes the need through its regulatory efforts and through comments submitted by interested persons.

Questions have been raised as to what FDA might consider acceptable ways of complying with certain requirements of the CGMP regulations, regarding the preparation of investigational new drug products for human or animal use. An investigational new drug product for human use is defined as a drug product (i.e., dosage form) covered by an investigational new drug

application (synonymous with a "Notice of Claimed Investigational Exemption for a New Drug"), Form FDA-1571, commonly referred to as an IND (21 CFR Part 312). An investigational new animal drug (INAD) is defined as a drug product (i.e., dosage form) covered by "A Notice of Claimed Investigational Exemption for a New Animal Drug" (21 CFR 511.1). The questions that have been raised concern, for the most part, the fact that product specifications and production methods for an investigational product may be subject to frequent change as the clinical testing of the product progresses.

FDA recognizes that manufacturing procedures and specifications will change as clinical trials advance. Analytical test methods may also be refined, or different methods used in response, for example, to formulation changes that interfere with some methods. However, as research nears completion, appropriate analytical methods should be well established and procedures and controls are expected to be more specific because they will have been based upon a growing body of scientific data and documentation. Questions have also been raised as to when, in the research and development of a new drug, a manufacturer must comply with the provisions of the CGMP regulations. During initial research and development, there is experimentation with the new drug substance and its dosage form; such experiments typically involve the drug's chemistry and toxicity studies conducted on laboratory animals. The CGMP regulations do not apply for the preparation of the new drug substance or drug products during such initial preclinical experimentation. However, it is nonetheless important to process materials under conditions to assure their integrity, and to maintain adequate records.

When drug development reaches the stage where the drug products are produced for clinical trials in humans or animals, then compliance with the CGMP regulations is required. For example, the drug product must be produced in a qualified facility, using laboratory and other equipment that has been qualified, and processes must be validated.

At early clinical stages, where a single batch of drug product may be produced, and where significant formulation and processing changes may make batch replication difficult or inexact, only limited process validation may be possible. In such cases, limited validation, especially for such critical processes as sterilization, should be derived, to the extent possible, from product and process analogs. In addition, data obtained from extensive in-process controls and intensive product testing may be used to demonstrate that the instant run yielded a finished product meeting all of its specifications and quality characteristics. It is expected that more comprehensive process validation will be conducted as additional uniform batches are made under replicated conditions.

There must also be written procedures for sanitation, calibration, and maintenance of equipment, and specific instructions for the use of the equipment and procedures used to manufacture the drug product.

FDA, while recognizing the differences between the manufacture of investigational products and commercial products, believes that it is nonetheless vital that investigational products be made in conformance with current good manufacturing practice. Product contamination and wide variations in potency can produce substantial levels of side effects and toxicity, and even produce wide-sweeping effects on the physiological activity of the drug. Product safety, quality, and uniformity are especially significant in the case of investigational products. Such factors may affect the outcome of a clinical investigation that will, in large measure, determine whether or not the product will be approved for wider distribution to the public.

Accordingly, FDA is committed to ensuring that investigational drug products are manufactured using adequate manufacturing facilities to ensure good quality control. In this regard, investigational drug products, like products approved for marketing, have always been subject to the agency's CGMP inspectional activities. The CGMP regulations, these inspectional activities, and this guideline apply to all such products, including investigational drug products intended for treatment use--see 21 CFR Part 312.

In this guideline, requirements of specific sections of 21 CFR Part 211 are presented along with practices and procedures that FDA believes may be useful to persons seeking to meet those requirements. This guideline does not attempt to address all sections of the regulations that apply to the preparation of investigational new drug products, but rather only those sections for which questions have been raised most frequently.

III. CONTROL OF COMPONENTS

Requirements

Section 211.80(a) requires, in part, control of components and drug product containers and closures by means of written procedures that detail handling, identification, sampling, testing, and storage.

Section 211.84(a) requires, in part, testing or examination as appropriate and approval of components, containers, and closures, before use.

Guidance

FDA recognizes that the experimental nature of the drug substance, formulation, and dosage form at an early stage of development will have an impact on establishing specifications. At early stages, the acceptance/rejection criteria may not be as specific; however, it is vital that such criteria be scientifically sound and based upon available scientific data. Specifications used as the basis for approval or rejection of components, containers, and closures will be more specific and uniform as additional data become available. It is vital that, at all stages, specifications used are fully documented.

IV. PRODUCTION AND PROCESS CONTROLS

Requirements

Section 211.100 requires, in part, that procedures that have a bearing on quality of drug products be written, be approved by the quality control unit, and be followed and documented in the execution of the production and process controls.

Guidance

During the IND stage of drug development, written production and control procedures are developed and initially may be more general because such procedures and controls are usually undergoing considerable refinement. However, initial procedures should be as complete and detailed as knowledge and experience with the product and dosage form permit. It is important that initial procedures be reviewed and approved prior to implementation, that they be followed, and that they be documented at the time of performance. It is vital that actual specific process control procedures and conditions such as timing, temperature, pressure, and adjustments (e.g., mixing, filtration, drying) be fully documented to permit review and approval by the quality control unit and to permit development of more specific written production and control procedures as research and development reach conclusion. It is essential that all changes from initial procedures be fully documented, and be based on well-founded scientific data or expert knowledge of a researcher having training and experience in the field of science being applied.

V. CALCULATION OF YIELD

Requirements

Section 211.103 requires calculations of actual yield and percentages of theoretical yield, at each appropriate phase of

the process. Further, it is required that the calculations be verified by a second person.

Section 211.186(b)(7) requires that master production and control records include a statement of theoretical yield along with limits on percentages of theoretical yield that trigger investigations of discrepancies.

Section 211.188(b)(7) requires that batch production records include statements of actual and percentage of theoretical yields at appropriate phases of processing.

Guidance

Significant differences between actual and theoretical yields can signal processing errors that result in mixups, superpotency, subpotency, and contamination. It is, therefore, essential to reconcile those differences. In the case of investigational new drugs, a variety of factors, such as the preparation of relatively small batch sizes and subdivision of in-process material for research purposes, may result in significant yield discrepancies. Those resulting discrepancies may not necessarily imply problems. However, even in the presence of such factors, yield discrepancies should be evaluated because other potential factors may have induced the discrepancies and may signal processing errors.

Specifications regarding theoretical yield that would trigger an investigation may initially be wider than at later stages of the drug product's development. However, it is vital that those initial specifications be established using the best information available , and that they assure a final product that meets identity, strength, and purity specifications. As clinical investigations progress and experience with production of the product increases, it is expected that these specifications will narrow, reaching levels that will be appropriate for full scale commercial production. Where yield discrepancies are significant or unexplained, it is essential that products not be released unless and until there is reconciliation of all materials used at each appropriate phase of production and other appropriate investigations have been conducted.

VI. EQUIPMENT IDENTIFICATION

Requirements

Section 211.105 requires, in part, that all compounding and storage containers, processing lines, and major equipment be identified to indicate their contents and, when necessary, the phase of production.

Guidance

FDA recognizes that investigational new drug products are sometimes prepared on a small scale basis, using equipment considerably downsized from devices used in commercial scale production. When such small scale equipment is used in an enclosed area, dedicated exclusively to one batch, adequate identification may be attained by a single sign used in a manner that appropriately identifies the material, stage of production, and batch number of the product.

Where several containers, each holding material at a different processing stage, are in proximity to each other (likely in small scale production), it is important that each container be appropriately identified in order to prevent mixups.

VII. PACKAGING AND LABELING OPERATIONS

Requirements

Section 211.130 requires, in part, that written procedures be designed and followed to assure that correct labels and labeling materials are used for drug products..

Section 211.130(b) requires a lot or control number (defined at § 210.3(b)(11)) for identification of the drug product.

Guidance

For investigational new drug products, certain labeling information may be provided separately from the drug container, where it is essential to the clinical study objectives that the drug(s) be provided as "blinded." In such cases a code-breaking guide is furnished to each investigator for emergency uses. FDA would not object if, for "blinding" purposes, the lot or control number is not visible on such containers but is provided separately for code-breaking purposes.

VIII. RESERVE SAMPLES

Requirements

Section 211.170(a) requires, in part, that a sample representative of each lot of each active ingredient be retained for at least 1 year after the expiration date of the last lot of drug product containing the active ingredient.

Section 211.170(b) requires, in part, that reserve samples of each lot of drug product be retained for at least 1 year after the expiration date.

Guidance

For investigational new drug products, a suggested retention time for reserve samples of active ingredients is the first to occur of the following:

(a) Two years after the date of termination or discontinuance of the relevant IND or INAD,

(b) Two years after the date of approval of the relevant new drug/new animal drug application, or

(c) One year past the expiration date of the last lot of drug product containing the active ingredient.

A suggested retention time for reserve samples of drug products is the first to occur of the following:

(a) Two years after the date of termination or discontinuance of the relevant IND or INAD,

(b) Two years after the date of approval of the relevant new drug/new animal drug application, or

(c) One year past the drug product expiration date.

IX. RECORDS RETENTION

Requirements

Section 211.180(a) requires, in part, that any production, control, or distribution record required by Part 211 and specifically related to a drug product batch be retained for 1 year past the expiration date of the batch.

Guidance

Production and control records related to batches of investigational new drug products may be retained for at least 2 years after the date of termination or discontinuance of the relevant IND, or at least 2 years after the date of approval of the relevant new drug application.