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.

508
509 **D. Sterile Products/Aseptically Processed Products**
510
511 We recommend that special precautions be taken for investigational new drugs intended to be
512 sterile. Thorough consideration should be given to controls for aseptic processing. The
513 following examples are recommendations that should be considered:
514
515 • Conducting aseptic manipulation in an aseptic workstation under laminar flow conditions
516 (e.g., an air classification of Class 100). Some examples of workstations include a
517 laminar air flow workbench, biosafety cabinets, or barrier isolator system.
518 • Disinfecting the entire aseptic workstation as appropriate (e.g., before aseptic
519 manipulation, or between different operations during the same day).
520
521 • Ensuring that items within a laminar airflow aseptic workstation not interrupt the airflow.
522
523 • Disinfecting gloves or changing them frequently when working in the laminar flow hood.
524
525 • Disinfecting the surface of nonsterile items (e.g., test tube rack, and the overwrap for
526 sterile syringes and filters) with sterile disinfectant solution before placing them in the
527 laminar flow hood.
528
529 • Performing manipulations of drug or components subsequent to a sterilizing step under
530 appropriate conditions.
531 • Documenting and following all procedures intended to maintain the sterility of the
532 components, in-process materials, and final product.
533 • Qualifying sterility tests (e.g., USP <71>) to demonstrate that the test article does not
534 interfere with the test.
535 • Employing aseptic technique and control of microbiological impurities in components
536 designed to prevent microbial and endotoxin contamination.
537 • Training personnel using aseptic techniques in those techniques.
538 • Qualifying for use equipment used for sterilization; performing appropriate calibration;
539 keeping maintenance records.
540 • Creating documentation to support the use of sterile components and disposable
541 equipment (e.g., filters, bags, containers) in the form of Sterilization/certification of
542 analysis, or demonstration that the sterilization method is validated.
543 • Ensuring that release of the final product by the QC unit, or person, include an acceptable
544 review of production records demonstrating that aseptic procedures and precautions were
545 followed.
546 • Ensuring that final products are not released until acceptable results of sterility testing are
547 known. We understand that products with a short shelf-life (e.g., radiopharmaceuticals,
548 cellular products) may have to be released while results of the sterility test are pending
549 based on results from other relevant tests (e.g., assessment of sterile filtration by bubble

point filter integrity test, cell product — a negative gram stain, or other rapid microbial detection test and negative endotoxin test)). We recommend that positive results from sterility or other relevant tests result in an investigation to determine the cause of contamination followed by corrective action if warranted.

554
555 # GLOSSARY
556
557 **Acceptance Criteria** - numerical limits, ranges, or other suitable measures for acceptance of test
558 results that the drug substance or drug products or materials at other stages of their manufacture
559 should meet
560
561 **Active Pharmaceutical Ingredient (API)** ***(or Drug Substance)*** - any substance or mixture of
562 substances intended to be used in the manufacture of a drug (medicinal) product and that, when
563 used in the production of a drug, becomes an active ingredient of the drug product. Such
564 substances are intended to furnish pharmacological activity or other direct effect in the diagnosis,
565 cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the
566 body.
567
568 **Batch** - a specific quantity of a drug or other material intended to have uniform character and
569 quality, within specified limits, and produced according to a single production order during the
570 same cycle of manufacture
571
572 **Component** - any ingredient intended for use in the manufacture of a drug product, including
573 those that may not appear in such drug product
574
575 **Contamination** - the undesired introduction of impurities of a chemical or microbiological
576 nature, or of foreign matter, into or onto a raw material, in-process material, or IND product
577 during production, sampling, packaging, or repackaging, storage or transport
578
579 **Cross-Contamination** - contamination of a material or IND product with another material or
580 product
581
582 **Drug product** - a finished dosage form (e.g., tablet, capsule, solution) that contains an active
583 drug ingredient generally, but not necessarily, in association with inactive ingredients. The term
584 also includes a finished dosage form that does not contain an active ingredient, but is intended to
585 be used as a placebo.
586
587 **In-process material** - any material fabricated, compounded, blended, or derived by chemical
588 reaction (e.g., intermediate) that is produced for, and used in, the preparation of the drug product
589
590 **Investigational new drug (IND product)** - a new drug or biological drug that is used in a
591 clinical trial. The term also includes a biological product that is used in vitro for diagnostic
592 purposes.
593
594 **Microdose studies** - studies in which participants are administered a single dose of less than
595 $1/100^{th}$ of the dose calculated to yield a pharmacological effect of the test substance based on
596 primary pharmacodynamic data obtained in vitro and in vivo (typically doses in, or below the
597 low microgram range) and at a maximum dose of ≤ 100 micrograms.
598
599

600 **Production** - all operations involved in the preparation of an IND product from receipt of
601 materials through distribution including processing, storage, packaging, labeling laboratory
602 testing and quality control
603
604 **Screening study** - a study that is performed under an exploratory IND application, is intended to
605 compare the properties of related active moieties to screen for the preferred compound or
606 formulations for additional clinical development under a traditional IND application.
607
608 **Specification** - a list of tests, references to analytical procedures, and appropriate acceptance criteria
609 that are numerical limits, ranges, or other criteria for the tests. It establishes the set of criteria to which a
610 drug substance or drug product should conform to be considered acceptable for its intended use.
611 *Conformance to specification* means that the material, when tested according to the listed
612 analytical procedures, will meet the listed acceptance criteria
613
614 **Sponsor** - person who takes responsibility for and initiates a clinical investigation
615
616 **Quality Units** - an organizational unit that fulfills quality control responsibilities. This can be in
617 the form of separate QC units or a single individual or group, depending upon the size and
618 structure of the organization.

619
620
621

## REFERENCES

622 1. FDA Guidance for Industry *Content and Format of Investigational New Drug*
623 *Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized,*
624 *Therapeutic, Biotechnology-derived Products.*

625 2. FDA Draft Guidance for Industry *Instructions and Template for Chemistry,*
626 *Manufacturing, and Control (CMC) Reviewers of Somatic Cellular Therapy*
627 *Investigational New Drug Applications (INDs)*, August 15, 2003

628 3. FDA Guidance for Industry *Instructions and Template for Chemistry, Manufacturing,*
629 *and Control (CMC) Reviewers of Human Gene Therapy Investigational New Drug*
630 *Applications (INDs)*, November 8, 2004.

631 4. FDA Guidance for Industry *Q7A Good Manufacturing Practice Guidance for Active*
632 *Pharmaceutical Ingredients*, Section 19

633

# Guidance for Industry, Investigators, and Reviewers

# Exploratory IND Studies

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**January 2006**
**Pharmacology/Toxicology**

*Contains Nonbinding Recommendations*

# Guidance for Industry, Investigators, and Reviewers

# Exploratory IND Studies

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*Contains Nonbinding Recommendations*

# Guidance for Industry and Reviewers[1]

# Exploratory IND Studies

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. Alternative approaches can be used if the approach satisfies the requirements of the applicable statutes and regulations. Discussions of an alternative approaches can be scheduled by contacting the FDA staff responsible for implementing this guidance. If the appropriate FDA staff cannot be located, contact can be made using the telephone number listed on the title page of this guidance.

## I. INTRODUCTION

This guidance is intended to clarify what preclinical and clinical approaches, as well as chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans, including studies of closely related drugs or therapeutic biological products, under an investigational new drug (IND) application (21 CFR 312). Existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in INDs than is required by regulations. This guidance is intended to clarify what manufacturing controls, preclinical testing, and clinical approaches can be considered when planning limited, early exploratory IND studies in humans.

For the purposes of this guidance the phrase *exploratory IND study* is intended to describe a clinical trial that

- is conducted early in phase 1,
- involves very limited human exposure, and
- has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).

[1] This guidance was developed by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER).

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collection of information in this guidance has been approved under OMB Control No. 0910-0014.

Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days). This guidance applies to early phase 1 clinical studies of investigational new drug and biological products that assess feasibility for further development of the drug or biological product.[2]

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

In its March 2004 *Critical Path Report*,[3] the Agency explained that to reduce the time and resources expended on candidate products that are unlikely to succeed,[4] new tools are needed to distinguish earlier in the process those candidates that hold promise from those that do not. This guidance describes some early phase 1 exploratory approaches that are consistent with regulatory requirements while maintaining needed human subject protection, but that involve fewer resources than is customary, enabling sponsors to move ahead more efficiently with the development of promising candidates.

### A. Traditional Phase 1 Approach

Typically, during pharmaceutical development, large numbers of molecules are generated with the goal of identifying the most promising candidates for further development. These molecules are generally structurally related, but can differ in important ways. Promising candidates are often selected using in vitro testing models that examine binding to receptors, effects on enzyme activities, toxic effects, or other in vitro pharmacologic parameters; these tests usually require only small amounts of the drug. Candidates that are not rejected during these early tests are prepared in greater quantities for in vivo animal testing for efficacy and safety. Commonly, a single candidate is selected for an IND application and introduction into human subjects, initially healthy volunteers in most cases.

Before the human studies can begin, an IND must be submitted to the Agency containing, among other things, information on any risks anticipated based on the results of pharmacologic and

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[2] Specifically, this guidance is limited to drug and certain well-characterized therapeutic biological products (e.g., recombinant therapeutic proteins and monoclonal antibodies) regulated by CDER. The guidance does not apply to human cell or tissue products, blood and blood proteins, vaccines, or to products regulated as devices.

[3] *Innovation or Stagnation, Challenge and Opportunity on the critical Path to New Medical Products* (March 2004).

[4] "A new medical compound entering phase 1 testing, often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market," *Critical Path Report*, March 2004.

toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). These basic safety tests are most often performed in rats and dogs. The studies are designed to permit the selection of a safe starting dose for humans, to gain an understanding of which organs may be the targets of toxicity, to estimate the margin of safety between a clinical and a toxic dose, and to predict pharmacokinetic and pharmacodynamic parameters. These early tests are usually resource intensive, requiring significant investment in product synthesis, animal use, laboratory analyses, and time. Many resources are invested in, and thus wasted on, candidate products that subsequently are found to have unacceptable profiles when evaluated in humans — less than 10 percent of INDs for new molecular entities (NME) progress beyond the investigational stage to submission of a marketing application (NDA).[3] In addition, animal testing does not always predict performance in humans, and potentially effective candidates may not be developed because of resource constraints.

Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with any IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility. As a result, limited, early phase 1 studies, such as those described in this guidance, are often supported by a more extensive preclinical database than is required by the regulations.

This guidance describes preclinical and clinical approaches, and the chemistry, manufacturing, and controls information that should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under a single IND application (21 CFR 312).

### B. Exploratory IND Approach

Exploratory IND studies usually involve very limited human exposure and have no therapeutic or diagnostic intent. Such studies can serve a number of useful goals. For example, an exploratory IND study can help sponsors

- Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme)
- Provide important information on pharmacokinetics (PK)
- Select the most promising lead product from a group of candidates[5] designed to interact with a particular therapeutic target in humans, based on PK or pharmacodynamic (PD) properties

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[5] For the purposes of this guidance, the term *candidate*, or *candidate product*, is used to describe a drug or biologic that is being tested in early exploratory studies under an IND. This guidance ***does not*** distinguish between a *drug product* and a *drug substance* as some other Agency guidances do.

(Most guidances use the term *drug product* to refer to a finished dosage form (e.g., tablet, capsule, solution) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients, or a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. *Drug substance* usually refers to any component that is intended to furnish pharmacological activity or other direct effect