

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 210

[Docket No. 2005N-0285]

DDM

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**Current Good Manufacturing Practice Regulation and Investigational New Drugs**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Direct final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending its current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational “Phase 1” drugs from complying with the requirements in FDA’s regulations. FDA will instead exercise oversight of production of these drugs under the agency’s general statutory CGMP authority and investigational new drug application (IND) authority. In addition, FDA is making available simultaneously with the publication of this direct final rule, a guidance document setting forth recommendations on approaches to CGMP compliance for the exempted Phase 1 drugs.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a companion proposed rule, under FDA’s usual procedure for notice-and-comment rulemaking, to provide a procedural framework to finalize the rule in the event the agency receives any significant adverse comments and withdraws this direct final rule. The companion proposed rule and direct final rule are substantively identical.

Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a draft guidance for industry entitled “INDs—Approaches to Complying With CGMP During Phase 1” to provide further guidance on the subject.

**DATES:** This rule is effective [*insert date 135 days after date of publication in the **Federal Register***]. Submit written or electronic comments on or before [*insert date 75 days after date of publication in the **Federal Register***]. If FDA receives no significant adverse comments within the specified comment period, the agency will publish a document confirming the effective date of the final rule in the **Federal Register** within 30 days after the comment period on this direct final rule ends. If timely significant adverse comments are received, the agency will publish a notice of significant adverse comment in the **Federal Register** withdrawing this direct final rule before [*insert date 105 days after date of publication in the **Federal Register***].

**ADDRESSES:** Submit written comments on the direct final rule to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** Monica Caphart, Center for Drug Evaluation and Research (HFD–320), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–9047; or Christopher Joneckis, Food and Drug Administration, Center for Biologics Evaluation and Research (HFM–1), 1401 Rockville Pike, Rockville, MD 20852, 301–435–5681.

**SUPPLEMENTARY INFORMATION:**

## I. Discussion

This action is intended to streamline and promote the drug development process while ensuring the safety and quality of the earliest stage investigational drug products, those intended for use in Phase 1 clinical trials. Together with its companion guidance, this rule represents a significant step in the agency's plan to formally lay out an approach to aid manufacturers in implementing manufacturing controls that are appropriate for this stage of development.

As defined in 21 CFR 312.21, a Phase 1 clinical trial includes the initial introduction of an investigational new drug into humans. Such studies are aimed at establishing basic safety and are designed to determine the metabolism and pharmacologic actions of the drug in humans. The total number of subjects in a Phase 1 study is limited—generally no more than 80 subjects. This is in contrast to Phase 2 and Phase 3 trials, which may involve substantially greater numbers of subjects being exposed to the drug product, and which aim to test the effectiveness of the drug product. During Phase 2 or 3, drug products may be made available for treatment use through one of several mechanisms for expanded access to investigational drugs.

FDA's general CGMP regulations for human drugs are set forth in parts 210 and 211 (21 CFR parts 210 and 211). Although the preamble to the September 1978 final rule issuing these regulations expressly stated that the CGMP regulations applied to investigational drug products, it also raised the possibility of proposing an additional CGMP regulation to cover drugs being used in research:

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 to cover drugs in research stages (43 FR 45014 at 45029, September 29, 1978).

Such additional regulations have never been issued.

In 1991, the agency issued a “Guideline on the Preparation of Investigational New Drug Products (Human and Animal).” That document, however, did not discuss all manufacturing scenarios, and did not clearly address small- or laboratory-scale production of drug products for use in Phase 1 clinical trials. Additionally, the 1991 guidance did not fully discuss the agency’s expectations on appropriate approaches to manufacturing controls for batches produced during drug development.

For several reasons, FDA believes that production of human drug products, including biological drug products, intended for use in Phase 1 clinical trials should be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211. First, even if exempted from the requirements of parts 210 and 211, investigational drugs remain subject to the statutory requirement that deems a drug adulterated:

if \*\*\* 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 \*\*\* [the Federal Food, Drug, and Cosmetic] Act as to safety and has the identity and

strength, and meets the quality and purity characteristics, which it purports or is represented to possess (21 U.S.C. 351(a)(2)(B)).

Second, FDA oversees drugs for use in Phase 1 trials through its existing IND authority. Every IND must contain, among other things, a section on chemistry, manufacturing, and control information that describes the composition, manufacture, and control of the investigational drug product (21 CFR 312.23(a)(7)). Submission of this information, along with other information required in the IND, informs the agency of the steps that the manufacturer is taking to ensure the safety and quality of the investigational drug. Under this IND authority, FDA has the option to place an IND on clinical hold if the study subjects would be exposed to an unreasonable and significant risk or if the IND does not contain sufficient information to assess the risks to subjects (21 CFR 312.42). FDA also may terminate an IND if the methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety (21 CFR 312.44(b)(iii)).

Thus, even though FDA is exempting Phase 1 drug products from compliance with the specific requirements of the CGMP regulations, the agency retains the ability to take appropriate actions to address manufacturing issues. For example, in addition to the authority to put an IND on clinical hold or terminate an IND, FDA may initiate an action to seize an investigational drug or enjoin its production if its production does not occur under conditions sufficient to ensure the identity, strength, quality, and purity of the drug, which may adversely affect its safety.

FDA believes this change in the CGMP regulations (parts 210 and 211) is appropriate because many of the issues presented by the production of investigational drugs intended for use in the relatively small Phase 1 clinical trials are different from issues presented by the production of drug products for use in the larger Phase 2 and Phase 3 clinical trials or for commercial marketing. We are considering additional guidance and regulations to clarify the agency's expectations with regard to fulfilling CGMP requirements when producing investigational drugs for Phase 2 and Phase 3 clinical studies.

Additionally, many of the specific requirements in the regulations in part 211 do not apply to the conditions under which many drugs for use in Phase 1 clinical trials are produced. For example, the concerns underlying the regulations' requirement for fully validated manufacturing processes, rotation of the stock for drug product containers, the repackaging and relabeling of drug products, and separate packaging and production areas are generally not concerns for these very limited production investigational drug products used in Phase 1 clinical trials. Consequently, in this direct final rule, FDA is amending the scope section of the drug CGMP regulations in 21 part 210 to make clear that production of investigational drugs for use in Phase 1 studies conducted under an IND does not need to comply with the regulations in part 211. However, once an investigational drug product has been manufactured by, or for, a sponsor and is available for use in a Phase 2 or Phase 3 study thus demonstrating an intent to expose more subjects to the investigational drug and requiring that the regulations' CGMP requirements be met, the same investigational drug product used in any subsequent Phase 1 study by the same sponsor must be manufactured in compliance with part 211. In addition to drug products that, if eventually approved, would be approved under section

505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355), this rule would apply to investigational biological products that are subject to the CGMP requirements of section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)). Examples of such products include recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood products, gene therapy products, and somatic cellular therapy products (including xenotransplantation products) that are subject to the CGMP requirements of section 501(a)(2)(B).

To convey the agency's current thinking on the possible approaches to manufacturing controls for the production of Phase 1 drugs, FDA is issuing simultaneously with this direct final rule a draft guidance titled "INDs—Approaches to Complying With CGMP During Phase 1," which sets forth recommendations on approaches to statutory compliance. Comments on that guidance can be submitted to the public docket identified in that document.

## **II. Direct Final Rulemaking**

FDA has determined that the subject of this rulemaking is suitable for a direct final rule. This direct final rule adds § 210.2(c) to make clear that production of an investigational drug for use in a Phase 1 study conducted under an IND, when the drug has not yet been, or is not being, manufactured for use in Phase 2 or 3 studies or for an already approved use, is not subject to the requirements in part 211. Additionally, the rule states that once an investigational drug product has already been manufactured and is available for use in Phase 2 or Phase 3 studies or for an already approved use, the investigational drug product used in any subsequent Phase 1 investigational studies must comply with part 211.

Because of the small batch size for these drugs, many of the issues implicated in larger scale production, which occurs late in the drug development process, or in commercial manufacture are not present during production of drugs for use in Phase 1 studies. The action taken should be noncontroversial, and the agency does not anticipate receiving any significant adverse comment on this rule.

If FDA does not receive significant adverse comment the agency will publish a document in the **Federal Register** confirming the effective date of the final rule. The agency intends to make the direct final rule effective 30 days after publication of the confirmation document in the **Federal Register**. A significant adverse comment is one that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. A comment recommending a rule change in addition to this rule will not be considered a significant adverse comment unless the comment also states why this rule would be ineffective without the additional change.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a companion proposed rule, identical in substance to the direct final rule, that provides a procedural framework from which to proceed with standard notice-and-comment rulemaking should the direct final rule be withdrawn because of significant adverse comment. The comment period for the direct final rule runs concurrently with that of the companion proposed rule. Any comments received under the companion proposed rule will be treated as comments regarding this direct final rule and vice versa. FDA will not provide additional opportunity for comment on the companion proposed rule. A full description of FDA's policy on direct final rule procedures may be found in a guidance

document published in the **Federal Register** of November 21, 1997 (62 FR 62466).

### **III. Legal Authority**

Under section 501(a)(2)(B) of the act (21 U.S.C. 201 *et seq.*) a drug is 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 in conformity with CGMP to ensure that such drug meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. The rulemaking authority conferred on FDA by Congress under the act permits the agency to amend its regulations as contemplated by this direct final rule. Section 701(a) of the act (21 U.S.C. 371(a)) gives FDA general rulemaking authority to issue regulations for the efficient enforcement of the act. We refer readers to the legal authority section of the preamble of the 1978 CGMP regulations for a fuller discussion (43 FR 45014 at 45020–45026).

### **IV. Environmental Impact**

The agency has determined that under 21 CFR 25.30(h) this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### **V. Analysis of Impacts**

FDA has examined the impacts of the direct final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental,

public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this direct final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of the rule on small entities. Because exempting production of drugs for use in Phase 1 studies from compliance with specific regulatory requirements does not add any burden, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$115 million using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The purpose of this direct final rule is to amend our current CGMP regulations to exempt the manufacture of Phase 1 drugs from compliance with the regulatory requirements in part 211. The rule will affect drug manufacturers, chemical manufacturers, and laboratories that manufacture drugs on a small scale for use in Phase 1 clinical trials.

For drug manufacturers that produce Phase 1 drug products in-house and also produce approved drug products, this direct final rule is expected to

reduce the amount of documentation they produce and maintain when they manufacture a Phase 1 drug. In some cases, it should also reduce the amount of component and product testing.

Because they have far less experience with pharmaceutical CGMPs, some chemical manufacturers and laboratories may experience a slight increase in documentation if they currently do not have written standard operating procedures (SOPs), or if they need to modify existing methods of documentation. Although formats may be different, the rule should not require more information than is already collected as part of standard laboratory practices.

Because the actual SOPs and manufacturing requirements are different for each new drug product and manufacturing facility, the procedures to comply with the statutory CGMP requirements for Phase 1 production are generated as part of product development. The savings or costs would be incurred on a per-IND and not per-facility basis.

This rule is intended to clarify requirements of the statutory CGMPs that are necessary for Phase 1 products and to exempt certain drugs produced under INDs from other CGMP requirements. Some manufacturers may realize savings because they no longer must meet certain requirements. The savings to drug manufacturers that produce the phase 1 drugs in-house will vary greatly from product to product. FDA lacks data to estimate the extent of cost savings. Some examples where substantial savings may be realized are the level of testing and analyzing components and in-process materials. These costs can typically range from \$50 to \$1,200 per component tested. The extent of the need for SOPs and methods validation may also be greatly reduced. We estimate that large drug manufacturers that produce Phase 1 drugs in-house could

potentially save between 24 to 40 hours per IND. In addition, the clarifications we have made could lead some large firms to produce future drugs for Phase 1 trials in-house, rather than contracting the work out.

For chemical manufacturers and laboratories, the requirements in this rule may increase the time required for developing SOPs for quality, process, and procedural controls and will be incurred on a recurring basis for each new product produced. There may also be an incremental increase in training costs to educate employees on the CGMP requirements. We estimate that an additional 12 to 24 hours may be required for these activities depending on the experience of the entity and its employees with our current CGMP rule.

The facility that manufactures the drug for the Phase 1 trials is identified in the IND. We do not keep a database of these facilities and, therefore, we do not have a precise number of entities that might be affected by this final rule. To estimate the economic impact, we derived an estimate of the number affected annually based on the number of INDs we receive.

In 2003, we received about 350 research and 500 commercial INDs. However, this rule would not apply to the majority of these INDs because they are for drug products that already have approvals and thus are subject to part 211. To derive an estimate of the percentage of INDs that would be affected by this rule, we used the percentage of total new drug applications (NDAs) that were for new molecular entities (NMEs) and applied that percentage to the number of annual IND applications. Historically, about 30 percent of NDAs are for NMEs each year. Assuming the relationship would be the same for the INDs and that the number of INDs will remain at about 850, this rule would affect about 255 INDs per year. A firm may produce multiple drug products for Phase 1 trials in a given year and use different companies to produce each

of these drugs. Therefore, we do not know how many individual entities would be affected by this rule each year.

The Small Business Administration (SBA) defines manufacturers of biologic drugs as small entities if they employ fewer than 500 people and other drug manufacturers as small if they employ fewer than 750 people. FDA estimates that about 65 percent of the entities that submit NDAs and biologics license applications to the agency meet SBA's definition of a small entity. We assume that the distribution of large to small entities that submit INDs would be about the same. Although many of the entities that produce drug products for Phase 1 trials are laboratories, they are usually part of much larger institutions and are not considered small under SBA's definition. All of the entities affected by this rule have personnel with the skills necessary to comply with the requirements.

Because we do not know the experience levels the affected entities have with our current CGMP requirements, we used the midpoint of the estimated ranges to estimate the potential recurring savings or costs.

Savings to large manufacturers from reduced SOP and validation requirements for Phase 1 drug production in-house, assuming a time savings of 32 hours per application, a fully loaded wage rate of \$45 and 90 INDs per year (approximately 35 percent of 255) would total \$129,600 per year or \$1,440 per IND. This would be in addition to any other savings from decreased component testing.

The incremental average annual cost to chemical manufacturers and laboratories, assuming all would incur costs and assuming an average increase of 18 hours per application for writing SOPs and training, a fully loaded wage

rate of \$45, and 165 INDs (approximately 65 percent of 255) affected per year, would total \$133,650 per year or \$810 per IND.

Although we do not know the number and size distribution of the entities affected by this rule, FDA believes that the impact on them will be negligible and should actually reduce the compliance burden for some. To clarify the requirements for the manufacture of drugs for Phase 1 trials, we have prepared a draft guidance document with recommendations for compliance.

## **VI. Paperwork Reduction Act of 1995**

This direct final rule contains no new information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Under the direct final rule, the production of human drug products, including biological drug products, intended for use in Phase 1 clinical trials will be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211. Parts 210 and 211 contain information collection requirements that have been approved by OMB under control number 0910–0139. As explained in the following paragraph, the information collection requirements in parts 210 and 211 will be reduced under this direct final rule.

The OMB-approved hourly burden to comply with the information collection requirements in parts 210 and 211 (control number 0910–0139) is 848,625 hours. FDA estimates that, under the direct final rule, approximately 7,315 drugs will be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211. Based on this number and the total number of drugs that are subject to parts 210 and 211, FDA estimates that the burden hours approved under control number 0910–0139 will be reduced by approximately 50,493 hours. Thus, as a result of the direct final

rule, the amended burden hours in control number 0910–0139 will be approximately 798,132 hours.

## **VII. Federalism**

FDA has analyzed this direct final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## **VIII. Request for Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## **List of Subjects in 21 CFR Part 210**

Drugs, Packaging and containers.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 210 is amended as follows:

**PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN  
MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS;  
GENERAL**

- 1. The authority citation for 21 CFR part 210 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

- 2. Section 210.2 is amended by adding paragraph (c) to read as follows:

**§ 210.2 Applicability of current good manufacturing practice regulations.**

\* \* \* \* \*

(c) An investigational drug for use in a Phase 1 study, as defined in § 312.21(a) of this chapter, is subject to the statutory requirements set forth at 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a Phase 1 study once the investigational drug has been made available for use by or for the sponsor in a Phase 2 or Phase 3 study, as defined in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a Phase 2 or 3 study or the drug has been lawfully marketed, the drug for use in the Phase 1 study must comply with part 211.

Dated: 1/9/06  
January 9, 2006.

*Jeffrey Shuren*

Jeffrey Shuren,  
Assistant Commissioner for Policy.

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