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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 210

[Docket No. FDA–2005–N–0170] (formerly Docket No. 2005N–0285)

Current Good Manufacturing Practice and Investigational New Drugs Intended for Use in Clinical Trials

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most phase 1 investigational drugs from complying with the regulatory CGMP requirements. FDA will continue to exercise oversight of the manufacture of these drugs under FDA's general statutory CGMP authority and through review of the investigational new drug applications (IND).

In addition, elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a guidance document entitled ''Guidance for Industry: CGMP for Phase 1 Investigational Drugs'' dated November 2007 (the companion guidance). This guidance document sets forth recommendations on approaches to compliance with statutory CGMP for the exempted phase 1 investigational drugs.

FDA is taking this action to focus a manufacturer's effort on applying CGMP that is appropriate and meaningful for the manufacture of the earliest stage investigational drug products intended for use in phase 1 clinical trials while ensuring safety and quality. This action will also streamline and promote the drug development process.

DATES: This rule is effective September 15, 2008.

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SUPPLEMENTARY INFORMATION:

I. Rulemaking Procedure

In the **Federal Register** of January 17, 2006 (71 FR 2458), FDA published a direct final rule to amend § 210.2 (21 CFR 210.2) to exempt most phase 1 investigational drugs from complying with the CGMP requirements in parts 210 and 211 (21 CFR parts 210 and 211). We explained that we issued this rule as a direct final rule because we believed it was non-controversial and that there was little likelihood of receiving significant adverse comments. We concurrently published in the **Federal Register** of January 17, 2006 (71 FR 2494) a companion proposed rule, identical in substance to the direct final rule, that provided a procedural framework from which to proceed with standard notice-and-comment rulemaking in the event we were required to withdraw the direct final rule because of significant adverse comments. A significant adverse comment is defined as a comment 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 change. Any comments received under the companion proposed rule were treated as comments regarding the direct final rule and vice versa. 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).

We received 14 comments on the proposed rule, of which several were considered to be significant adverse comments. Therefore, in the **Federal Register** of May 2, 2006 (71 FR 25747), we withdrew the direct final rule. This final rule summarizes and responds to the comments received on the direct final rule and proposed rule. See section V of this document for a discussion of the comments and FDA's responses.

Together with the companion guidance, this final rule will assist the drug development process by streamlining the application of CGMP that is more appropriate to the manufacture of the earliest stage investigational drug products—those intended for use in phase 1 clinical trials.

II. Background

A phase 1 clinical trial includes the initial introduction of an investigational new drug product, including biological drug products, into humans. Such studies are conducted to establish the basic safety of the drug, and are designed to determine the metabolism and pharmacologic actions of the drug in humans. The total number of subjects in a phase 1 clinical trial is limited generally to no more than 80 subjects. This is in contrast to phase 2 and phase 3 clinical trials when a substantially greater number of subjects are involved, more subjects are exposed to the drug product, and the effectiveness of the drug product is also tested in addition to safety. During phase 2 or phase 3, drug products may also 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. Although the preamble to a final rule published in the **Federal Register** of September 29, 1978 (43 FR 45014) (the 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 specifically designed to cover drugs in research stages'' (43 FR 45014 at 45029). Such additional regulations have never been issued.

On February 21, 1991, FDA issued a guidance document entitled ''Preparation of Investigational New Drug Products (Human and Animal)'' (56 FR 7048) (the 1991 guidance). 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 FDA'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 (phase 1 investigational drugs) 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 practices to assure that such drug meets the requirements of this chapter [of the Federal Food, Drug, and Cosmetic Act (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'' (section 501(a)(2)(B) of the act (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 (§ 312.23(a)(7) (21 CFR 312.23(a)(7))). Submission of this information, along with other information required in the IND, informs FDA 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 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)(1)(iii)).

Thus, even though FDA is exempting phase 1 drug products from compliance with the specific requirements of the CGMP regulations, FDA 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 FDA's expectations with regard to fulfilling CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical trials.

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 final rule, FDA is amending the scope section of the drug CGMP regulations in part 210 to make clear that production of investigational drugs for use in phase 1 clinical trials 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 act (21 U.S.C. 355), this rule applies to investigational biological products that are subject to the CGMP requirements of section 501(a)(2)(B) of the act. Examples of such products include recombinant and non-recombinant 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) of the act. Therefore, this final rule exempts the production of phase 1 investigational drugs from complying with the regulatory requirements set forth in parts 210 and 211.

III. Legal Authority

Under section 501(a)(2)(B) of the act, 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, CGMPs 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 FDA to amend its regulations as contemplated by this final rule. Section 701(a) of the act (21 U.S.C. 371(a)) gives FDA, through delegation from the Secretary of the Department of Health and Human Services, general rulemaking authority to issue regulations for the efficient enforcement of the act. We refer readers to section V of the preamble of the 1978 final rule for a fuller discussion of our CGMP rulemaking authority (43 FR 45014 at 45020–45026).

IV. Summary of the Final Rule

This final rule adds paragraph (c) to § 210.2, exempting certain investigational drugs for use in a phase 1 clinical trial (including biological drugs) from compliance with part 211. However, these drugs remain subject to the statutory requirements under section 501(a)(2)(B) of the act, i.e., CGMP. The regulation also explains that the exemption from compliance with part 211 does not apply to an investigational drug that a sponsor has made available

for a phase 2 or phase 3 clinical trial, or has lawfully been marketed, and is being used for a phase 1 clinical trial. Such investigational drug products used for a phase 1 clinical trial must comply with part 211.

We have also changed the term ''defined'' to ''described'' for clarification.

V. Comments on the Proposed Rule and FDA's Responses

We received approximately 14 comments on the proposed rule. Several comments were duplicate submissions by the same entity; several other comments submitted to the docket pertained to the draft guidance under a separate docket number. These comments were also considered in revising the draft guidance. The following responses are specific to the comments on the proposed rule.

A. General Comments

(Comment 1) Several comments welcome the proposed changes and commend FDA for revising the regulations to exempt phase 1 investigational drugs from regulatory CGMP under part 211. One comment adds that, because most products do not proceed beyond the clinical trial phase of development, the burden of full compliance with CGMP at the phase 1 stage far outweighs any perceived benefit and suggests that FDA devise a progressive scale for CGMP compliance beginning with phase 1 clinical trials through approval to market the product.

(Response) We appreciate these supportive comments. Our expectation in issuing this final rule is that sponsors will take an appropriate approach to instituting manufacturing controls appropriate for the stage of investigational drug development.

(Comment 2) Some comments oppose exempting phase 1 investigational drugs from compliance with part 211 because they are concerned that there could be an effect on product safety and human subject protection. Another comment believes that FDA's proposed approach to exempt phase 1 investigational drugs from the applicability of part 211 not only invites greatly reduced product standards, but affects FDA's ability to take remedial action. One reason given was that FDA does not have the personnel to monitor the manufacture of phase 1 investigational drugs during clinical trials. Another comment believes that if the phase 1 investigational drugs are not reproducible, not well-documented, or not well-controlled, the results of the trial will be meaningless and delay availability of new drugs for commercial use. The comment continued to state that an establishment could interpret FDA's proposal as loosening the basic requirements needed for phase 1 material, which would not only jeopardize patients and the results of the phase 1 clinical trial, but also the investigational stages of development that follow.

(Response) We are confident that exempting phase 1 investigational drugs from the CGMP regulations in part 211 will not jeopardize product safety or human subject protection. This action is intended to focus a manufacturer's effort on applying CGMP that is appropriate and meaningful for the manufacture of the earliest stage investigational drug products intended for use in phase 1 clinical trials, while also ensuring the products' safety and quality. An additional consequence of this action is to streamline and promote the drug development process. The companion guidance provides our current thinking on ways to comply, through the use of specified quality controls, with statutory CGMP for the production of phase 1 investigational drugs. As previously described, we will continue to oversee product safety and human subject protection through articulation of statutory CGMP requirements, clarified in the companion guidance, and a thorough review of the chemistry, manufacturing, and control information submitted in the IND application for identity, quality, purity, strength, and potency of the investigational drug necessary to ensure the safety of the subjects in the phase 1 clinical trial. We believe that this exemption does not ''loosen'' the requirements, but establishes quality control principles that are appropriate and comprehensive for the manufacture of phase 1 investigational drugs, i.e., interpreting and implementing CGMP consistent with good scientific methodology.

We also believe that the exemption will not affect or change our ability to take remedial action if necessary, or to monitor the manufacture of such investigational drugs; nor do we believe that this action will delay availability of new drugs for commercial use. As stated elsewhere in this document and in the proposed rule, compliance with CGMP is required by section 501(a)(2)(B) of the act and a drug can be deemed adulterated by FDA for failure to comply with statutorily mandated CGMP.

(Comment 3) One comment states that the proposed rule was misleading and unclear. The comment asserts, correctly, that a phase 1 investigational drug used in phase 2 and phase 3 clinical trials must comply with part 211, but argues that the progression of the study to phase 2 and phase 3 is unknown at the time of the phase 1 investigational drug production. Therefore, the sponsor will most likely produce the phase 1 investigational drug in compliance with part 211 in lieu of not being able to use data from the phase 1 study for phase 2 and phase 3.

(Response) We disagree that the proposed rule was misleading and unclear. In the preamble to the direct final rule (71 FR 2458 at 2459), we explained that we believe the exemption for phase 1 investigational drugs ''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.'' Given the differences between phase 1 clinical trials and phase 2 and phase 3 clinical trials discussed in section II of this document, we believe compliance with the particular regulations in part 211 is not appropriate for phase 1 investigational drugs because many of the specific requirements in part 211 do not apply to the manufacture of phase 1 investigational drugs in the same manner because they were intended to apply to commercial drug manufacture. For example, rotation of the stock for drug product containers, the repackaging and relabeling of drug products, and separate packaging and manufacturing areas are generally not of concern for the limited production of phase 1 investigational drugs. Additionally, the requirement for fully validated manufacturing processes may not be appropriate for this early stage of development. We believe that recommending approaches and considerations, and allowing the manufacturer to develop specific controls appropriate for the particular product, manufacturing process, and facility in order to comply with statutory CGMP requirement is less burdensome and more efficient for the sponsor. We agree that drug products used in phase 2 and phase 3 clinical trials may be improved or refined (i.e., manufacturing process and/or product) based on the results of the phase 1 clinical trial. However, limiting the exemption from compliance with the regulations in part 211 to drugs for use in phase 1 clinical trials (and not extending it to drugs that a sponsor has made available for a phase 2 or phase 3 clinical trial, or has lawfully marketed) does not preclude the use of

data from a phase 1 clinical trial for phase 2 and phase 3. While it is true that some sponsors may choose to manufacture phase 1 investigational drugs in compliance with the regulatory requirements in part 211 in anticipation of expansion of the product into phase 2 clinical trials, this rule does not require that they do so, and it is up to the manufacturer to determine whether it makes sense in their particular case to manufacture the phase 1 drug in compliance with the regulations in part 211.

(Comment 4) One comment states that FDA is ignoring past reports of phase 1 clinical trial failure, i.e., the two subject deaths in phase 1 clinical trials conducted at Johns Hopkins University and the University of Pennsylvania, and the six subjects who experienced major organ failure in a phase 1 clinical trial in England. The comment also adds that there have been several deaths and recalls due to drugs compounded by pharmacists and an increase of recalls of medical devices due to CGMP noncompliance. The comment also makes the statement that FDA should not assume that a medical researcher or other employee would be able to make safe phase 1 materials following guidance.

(Response) We disagree with the comment highlighting the cases as a reason for not issuing this final rule. Investigations of the referenced cases found no evidence to suggest that the adverse events were caused by the manufacturing of the phase 1 investigational drug (Refs. 1, 2, and 3), and neither the British not the Johns Hopkins studies had been submitted to FDA under IND, and so had consequently not been prospectively reviewed by FDA (See *http://www.fda.gov/cder/warn/2003/02–hfd–45–0303.pdf*), and thus, we are of the opinion that nothing in this final rule would have affected the outcome of any of the specific cases mentioned as we are not aware that CGMP was deficient or contributed to the deaths. As to the implication in the comment that these three cases indicate that there are risks in the manufacture of drugs for use in phase 1 clinical trials, we believe that there is risk in the manufacture of any drug, whether investigational or not and regardless of the stage of testing. We note, again, that investigational drugs for use in phase 1 clinical trials remain subject to statutory CGMP, and a companion guidance is being issued concurrent with this rule to provide suggested approaches for complying with statutory CGMP for phase 1 investigational drugs.

With regard to the comment on pharmacy compounding errors, the reported instances of recalls due to drugs compounded by pharmacists are not analogous to producing drugs for phase 1 clinical trials, which is the subject of this rulemaking. Moreover, the comment concerning an increase of medical device recalls due to CGMP noncompliance apparently assumes that this final rule relieves phase 1 investigational drugs of compliance with any CGMP requirements. However, as previously discussed, this final rule exempts phase 1 investigational drugs only from regulatory CGMP requirements in parts 210 and 211. The statutory requirement to comply with CGMP still applies. We note that, in addition to the considerations described in the guidance, reference to technical information and appropriate training are necessary to comply with statutory CGMP.

B. CGMP Regulation Specific to Phase 1 Investigational Drugs

(Comment 5) Several comments request that FDA engage stakeholders and issue a new rulemaking for CGMP specific to phase 1 investigational drugs. One comment suggests that FDA apply the comments submitted to the docket on the proposed rule and draft guidance in proposing a new rule. Another comment suggests that FDA amend only the relevant requirements, e.g., on the repackaging and relabeling of drug products, retaining the oversight in all phases of a clinical trial of a drug.

(Response) We appreciate the comments and will consider the appropriateness of such a proposed rule. For current purposes, however, we intend to proceed directly from the statute, and direct the public to the companion guidance that is being issued concurrently with this rule, suggesting some approaches to comply with statutory CGMP for phase 1 investigational drugs.

C. Scope

(Comment 6) One comment requests FDA to clarify the scope of the rulemaking, i.e., that the scope does not include active pharmaceutical ingredients (API).

(Response) The scope of the exemption from compliance with part 211 includes investigational new human drug and biological products, including finished dosage forms used as placebos, for human use in a phase 1 study or trial. Examples of such investigational drugs include, but are not limited to, the following:

- Investigational recombinant and non-recombinant therapeutic products,
- Vaccine products,
- Allergenic products,
- In vivo diagnostic products,
- Plasma derivative products,
- Blood and blood components[1],
- Gene therapy products, and
- Somatic cellular therapy products (including xenotransplantation products).

However, if such products have already been manufactured by an IND sponsor for use during phase 2 or phase 3 clinical trials or have been lawfully marketed, the manufacture of such a product must comply with the appropriate requirements of part 211 for the product to be used in any subsequent phase 1 clinical trial, irrespective of the trial size or duration of dosing.

Manufacturers of new active pharmaceutical ingredients (also referred to as ''API'' or ''drug substance'') are already exempt from compliance with part 211 and must also conform with CGMP as required in section 501(a)(2)(B) of the act. Thus, this rule does not change in any way how APIs are regulated with regard to CGMP. As stated in the companion guidance, limited guidance on CGMP for the manufacture of new API for some IND products used in clinical trials is also available (see International Conference on Harmonisation (ICH) Q7A GMP Guide for API (ICH Q7A guidance)). Manufacturers of APIs should implement controls appropriate to the stage of development and, thus, should also consider the recommendations described in the companion guidance for manufacture of API used in investigational drug products for phase 1 clinical trials.

(Comment 7) In the direct final rule, FDA makes the statement ''[T]his action is intended to streamline and promote the drug development process'' (71 FR 2458 at 2459). One comment believes that this proposal is outside the scope of FDA's mission mandated by Congress, i.e., to ''promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner'' and ''with respect to such products, protect the public health by ensuring that * * * human and veterinary drugs are safe and effective.'' The comment

[1] You should consult with the Office of Blood Research and Review, Center for Biologics Evaluation and Research (CBER), to determine circumstances when an IND would be required for blood or a blood component. Manufacturers of blood and blood components intended for transfusion and for further manufacture must still comply with the applicable regulations in 21 CFR parts 600 through 660.

further states that FDA was established to serve as a consumer protection agency and a check and balance on regulated industry.

(Response) As section III of this document notes, CGMP is required by section 501(a)(2)(B) of the act, and FDA has been given the general authority to issue regulations for the efficient enforcement of the act. We note here as well that, under section 505(i) of the act, FDA is directed to issue regulations for exempting from the requirements of section 505 ''drugs intended solely for investigational use by experts qualified by scientific training and experience to investigation the safety and effectiveness of drugs,'' which include drugs for use in phase 1 clinical trials. While we agree that FDA is an agency whose public health mission demands an emphasis on safety, we note that this does not require us to impose burdens on drug development that do not have a commensurate public health benefit. We believe that this final rule is appropriate because many of the regulatory requirements in part 211 simply are not applicable to the manufacture of products intended for use in phase 1 clinical trials, and that the agency can continue to protect human subjects via interpretation of statutory CGMP and the IND process.

D. Direct Final Rule and Companion Proposed Rule Approach

(Comment 8) A couple of comments object to the direct final rule/companion proposed rule approach (rulemaking approach). One comment believes that the process did not allow for a discussion regarding the quality of clinical trial material, i.e., the establishment of meaningful, consistent standards that balance patient protection with speed of development. The comment then suggests that FDA work with industry to address industry-wide questions about quality for clinical trial materials, e.g., equipment qualification, water quality, method validation or qualification, sterility assurance, control of contractors, complaints, cleaning, and specifications.

(Response) We disagree with the assertion that we did not allow for a discussion regarding the quality of clinical trial material. In developing the companion guidance, we utilized our experience with IND submissions and facility inspections. In addition, comments submitted to the docket were considered in finalizing the rule and the companion guidance, as well as stakeholder comments provided in multiple venues where FDA representatives discussed the proposed rule and draft guidance. Both the companion guidance and relevant IND regulations emphasize safety as the primary focus of phase 1 clinical trials. The companion guidance is written to allow for flexibility in utilizing appropriate CGMP controls for the product, manufacturing process, and facility to assure product safety. We will continue to work with stakeholders to refine appropriate standards as needed through continued discussions and meetings in various venues with stakeholders.

(Comment 9) One comment states that FDA does not have the expertise to issue guidance or regulation without stakeholder input and adds that the manufacture of clinical supplies is a complex matter in which FDA has almost no experience. The comment also states that FDA lacks expertise in clinical GMP compliance because FDA has performed few inspections of early clinical supply material.

(Response) We disagree with this comment. The decision to generate guidance for this early phase of clinical trial manufacture was due primarily to the constant requests for guidance in this area from the pharmaceutical industry, academia, and other research organizations. The publication of the draft guidance and the direct final and proposed rules in January 2006 was to address this apparent need, and to seek broader stakeholder input. Additionally, we have experience from numerous sources, such as participation with stakeholders in related workshops and conferences, facility inspections, and other interactions that result in sufficient understanding necessary to issue rulemaking and companion guidance. Contrary to the suggestion of the comment, conducting inspections of early clinical trial material is not the exclusive source of FDA expertise in this area.

(Comment 10) One comment believes that FDA's finding that the subject is suitable for this rulemaking approach is based on assumptions, not data, such as the results of ''for cause'' inspections, treatment IND inspections, or reports of adverse drug events occurring during phase 1 clinical trials.

(Response) We disagree with the comment. In the direct final rule, we stated that the rulemaking approach is appropriate because many of the issues present in the manufacture of phase 1 investigational drugs are different from those issues presented by the manufacture of drugs for later investigational phases or for commercial marketing, and that many of the specific requirements in part 211 are not applicable in the manufacture of the smaller batches of investigational drugs usually used in phase 1. These statements are not based on assumptions, as the comment suggests, but on the knowledge of, and experience with, good manufacturing practice for phase 1 investigational drugs.

(Comment 11) One comment states that the proponents of the rulemaking approach cite the successful use of ICH Q7A guidance and its use during inspections without the need for a regulation. The comment suggests that the possible reason for the successful use is that the ICH Q7A guidance is more detailed than the draft guidance and is used to manufacture material that is further processed before being delivered to patients.

(Response) We disagree with the comment. Due to the more defined routes of manufacture of APIs, and the general application of CGMP to APIs in the companion guidance, the ICH Q7A guidance was able to provide more detail for the commercial manufacture of APIs. Early phase clinical trial material may use many different routes of manufacture, some of which may be new and innovative. In addition, the recommendations or expectations contained in the ICH Q7A guidance (see section XIX of that guidance, on APIs for use in clinical trials) utilize an approach to CGMP similar to that outlined in the companion guidance. For the reason stated in response to comment 4, we believe that the companion guidance provides adequate considerations when supplemented with additional technical information and appropriate training to comply with CGMP.

E. Exemption From Part 211

(Comment 12) One comment believes that compliance with statutory CGMP requirements and exemption of phase 1 investigational drugs from the requirements in part 211 subjects phase 1 investigational drugs to unwritten standards, developed case-by-case without any input from the public or industry. The comment also states that unwritten standards would lead to differing interpretations within FDA, e.g., by individual investigators, district offices, and review divisions. Inconsistency, non-transparency, and uncertainty slow product development as the industry tries to comply on a shifting landscape of uncertain legal basis.

(Response) We disagree with the comment. We believe that we have provided sufficient opportunity for the public and industry to comment on the proposed exemption of phase 1 investigational drugs from compliance

with part 211, the draft guidance, and the impact of such action. The purpose of the companion guidance is to provide recommendations for compliance with statutory CGMP and to promote consistency in compliance. The companion guidance is intended for use not only by industry, but also by FDA staff to assist in fulfilling their review and enforcement responsibilities. It bears emphasis that, because FDA has set forth its interpretation of some acceptable approaches to statutory CGMP in the companion guidance, as opposed to a rule, we remain open to alternative approaches to compliance, so long as they provide comparable safety and protection for human subjects. We believe this approach maximizes flexibility and minimizes burden, without diminishing safety protections.

(Comment 13) One comment states that unclear rules erode quality. For example, financially strapped companies will not be able to justify expenses based on recommendations in a draft guidance. Inevitably, some companies will stumble, and quality will drop.

(Response) Industry is not obligated to implement draft guidance. Draft guidance is for the purpose of soliciting comments on FDA's current thinking on a subject.

In § 10.115(d)(1) (21 CFR 10.115(d)(1)), we explain that guidance does not legally bind the public or FDA. Therefore, a financially strapped company may choose to use a less expensive approach other than the one recommended in a guidance, but the alternative approach must comply with the relevant statutes and regulations in assuring patient safety, and the company would be prudent to consult FDA before using the alternative approach. As previously stated in our response to comment 12, we believe this rule maximizes flexibility and minimizes burden without diminishing safety protections.

(Comment 14) One comment believes that regulatory CGMP provides minimum, legal requirements to safely make drugs or biologics made for use in humans. Another comment states that, instead of the detailed, enforceable standards laid out in part 211, FDA proposes to rely upon three sources of authority that are variously lacking in detail and/or enforceability, i.e., the statutory authority (section 501(a)(2)(B) of the act), the IND submission requirements in § 312.23, and the draft guidance.

(Response) We disagree with this comment, and believe the comment confuses the requirements of the statute and the regulations. Many of the regulatory requirements in part 211 are not readily applicable to the manufacture of investigational drugs for use in phase I clinical trials. As previously stated, because such products still must comply with statutory CGMP, and because FDA has offered suggestions for acceptable methods for complying with statutory CGMP, we believe that manufacturers will have sufficient guidance to know what they must do to safely make drugs or biologics for such early stage clinical trial use in humans. We dispute the assertion that we are eschewing detailed, enforceable standards in favor of relying upon three sources of authority that are variously lacking in detail and/or enforceability. Statutory CGMP remains enforceable and we are issuing a companion guidance that details acceptable approaches for complying with statutory CGMP, and FDA's authority to place clinical trials on hold (under its IND authority) remains unchanged.

(Comment 15) One comment states that FDA assumes that, once this rulemaking is final and phase 1 investigational drugs are exempt from complying with part 211, new sponsors would keep proper records, perform necessary testing, or keep retention samples for later investigations, or that they would take the time to learn and follow CGMP if there were no regulations requiring them to do so. Another comment states that FDA, without evidence, claims that having to actually produce drug or biological products according to accepted international standards is a barrier too high for entry into phase 1 studies. The comment continues to say that such barriers do serve a social purpose, i.e., preventing those incapable of following or unwilling to follow CGMP from administering investigational products to humans.

(Response) As mentioned in the preamble to the proposed rule and draft companion guidance, application of part 211 is not appropriate to the production of IND products used in phase 1 studies. The type and extent of CGMP for investigational studies differs from those typically employed for routine commercial manufacturing, and in some cases may even include more stringent controls for certain manufacturing operations of investigational products. We believe that the proposed rule and the draft companion guidance better communicate FDA expectations and facilitates compliance with CGMP for the production of phase 1 investigational drugs rather than trying to apply existing part 211 regulations. Our expectation that phase 1 investigational drugs be manufactured following appropriate CGMP in adequate manufacturing facilities has not diminished with the adoption of this approach.

FDA is not claiming that the manufacture of a drug or biological product for use in phase 1 studies according to international standards presents too high a barrier. FDA's position is that the United States' good manufacturing practice regulations were written primarily to address commercial manufacturing and do not consider the differences between early clinical supply manufacture and commercial manufacture. The final rule and companion guidance are intended to address these differences, while still requiring all drugs for human consumption, including those used in clinical trials, to be manufactured in accordance with CGMP as required by section 501(a)(2)(B) of the act.

F. Risk to Patients

(Comment 16) One comment maintains that FDA understates the risk to patients. The comment continues to say that the CGMP regulations are designed to protect patients from mishaps that would have major impact on the clinical subject, e.g., contamination with bacteria, penicillin, or industrial cleaning agents; and product mix-ups. Another comment believes that § 312.23, which requires companies to submit information about the clinical material, has nonexistent patient protections, and that submitting general information is no substitute for compliance with CGMP.

(Response) We disagree with the assertion that we understated the risk to subjects (patients). We believe that there is no additional risk to subjects with this exemption, and have provided recommendations that interpret and implement CGMP consistent with good scientific methodology. In complying with section 501(a)(2)(B) of the act, a manufacturer must manufacture the drug in conformity with good manufacturing practice to assure that the 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. If the drug does not meet these criteria, the drug is considered adulterated and therefore a possible risk to subjects. Because the statutory requirements allow for flexibility in describing CGMP, we have issued the companion guidance to recommend CGMP for phase 1 investigational drugs. These recommended quality controls for

producing a phase 1 investigational drug are specifically designed to ensure subject safety.

(Comment 17) One comment believes that the exemption of phase 1 investigational drugs from part 211 puts patients at risk because it is difficult to prove what CGMP is, and makes it difficult for FDA to investigate or prosecute serious cases. The comment also states that a quality assurance (QA) unit is required for preclinical studies and a quality control (QC) unit is required for phase 2 and phase 3 studies. However, the new approach does not provide for a QA or QC unit for phase 1 studies.

(Response) We disagree with this comment. As previously discussed in section II of this document, CGMP consists of steps that a manufacturer takes to ensure the safety and quality of the investigational drug. This information is submitted to FDA in the IND. Through FDA's IND authority, FDA has the ability to take appropriate actions to address manufacturing issues if there is a safety risk to subjects, i.e., place an IND on clinical hold, terminate an IND, seize an investigational drug, or prohibit its production.

The functions performed by QA and/or QC unit(s) appropriate for this early phase of clinical trial material manufacture were clearly spelled out in the draft companion guidance. We describe in the companion guidance the QC functions that should be in effect to manufacture in compliance with CGMP for phase 1 clinical trials. It is at the discretion of the manufacturer if it wishes to implement these responsibilities through separate QA and QC groups.

(Comment 18) One comment asserts that if the study subjects are exposed to unreasonable and significant risk or if the IND does not contain sufficient information to assess risk to patients, any action by FDA, i.e., placing a clinical hold or terminating an IND, would occur after the fact and well after patients are injured in the trial.

(Response) Sponsors must inform the subjects of clinical trials of inherent, unknown risks (21 CFR 50.25). FDA will typically place a clinical hold or terminate an IND as a result of evaluating safety information provided as part of the IND review. Such evaluations are conducted prior to the initiation of the clinical trial. Therefore, we can and will, when appropriate, take such actions before the clinical trial proceeds. In addition to taking action before the clinical trial begins, we also have the ability under statutory CGMP to take enforcement actions once the phase 1 clinical trial begins.

(Comment 19) One comment points out that FDA recognizes that, although part 211 applies to phase 2 and phase 3 investigational drugs, the extent of the controls varies based on the phase of the clinical study. The comments also state that FDA agrees that not all sections of part 211 may apply to phase 2 and phase 3 investigational drugs. For this reason, the comment suggests revising the last sentence of proposed § 210.2(c) to require that the drug for use in phase 1 study comply with the appropriate sections of part 211. Another comment also provided alternative language to § 210.2(c) stating that if the investigational drug has been made available for a phase 2 or phase 3 study or the drug has been lawfully marketed, and the manufacturer needs to conduct further phase 1 studies to generate data to support the registration of the clinical indication being developed, the drug used in the phase 1 clinical trial need not comply with part 211.

(Response) We disagree with the comment. Because of the wide variability in the possible manufacturing processes used to produce early phase clinical trial material, it is not feasible to specify what parts of part 211 are appropriate in a companion guidance, because what may be appropriate for one manufacturing situation may be inappropriate for another.

We decline to use the alternative codified language proposed by the comment, which would exempt from the requirements of parts 210 and 211 investigational drugs used in phase 1 clinical trials where the drugs have been lawfully marketed or used in phase 2 or phase 3 clinical trials. Because the drug products in question have already been manufactured using CGMP as indicated in part 211, the manufacturing knowledge is already available and should be fully utilized.

(Comment 20) One comment reiterates the proposal that phase 1 investigational drugs would be manufactured following statutory requirements and recommendations through guidance for CGMP, and if used for a phase 1 clinical trial after available for phase 2 and phase 3 clinical trials or marketed, the phase 1 material would be manufactured using regulatory CGMP. The comment raises the question of the possibility that the phase 1 investigational drugs not manufactured per the same standard and used on human subjects is unethical. Another comment suggests that if only certain phase 1 investigational drugs follow CGMP while others are exempt it promotes a situation where subject safety may be at risk.

(Response) We believe that the comment fails to recognize that the scope of the specific recommendations for CGMP in support of the statutory requirements provides the same, if not additional, protection of the phase 1 clinical trial subject. Given that FDA retains oversight over these part 211-exempt phase 1 products via the IND mechanism, and that the agency is issuing guidance on ways to comply with statutory CGMP in the manufacture of such products, we firmly believe that this rule presents no safety or ethical issue. However, as discussed elsewhere in this preamble, we are requiring that phase 1 investigational drugs that the sponsor makes available for phase 2 and phase 3 clinical trials or as lawfully marketed drugs comply with part 211. This is because, given the manufacturing scale of a product that will be administered beyond a phase 1 trial, such products are more like products manufactured for use in phase 2 and phase 3 clinical trials or lawfully marketed drugs. The fact that we are requiring investigational drugs manufactured in significant enough quantities that they are available for phase 2 or phase 3 testing or lawful marketing to comply with regulatory CGMP, does not mean that product that is manufactured only for use in a phase 1 trial, and is thus exempt from complying with regulatory CGMP, is unsafe. The current rulemaking exempting products from compliance with part 211 is limited to products manufactured exclusively for use in a phase 1 trial and the fact that some products used in phase 1 trials will be manufactured in compliance with the requirements of part 211 does not mean that products that are not so manufactured in compliance with statutory CGMP are unsafe.

G. Use of Guidance

(Comment 21) One comment believes that FDA should not use guidance in place of minimum CGMP requirements for the safe manufacture of drugs or biologics for human beings. Another comment requests that FDA not exempt the manufacture of phase 1 investigational drugs from part 211, but instead issue guidance to help manufacturers find innovative, simple, and inexpensive approaches to comply with CGMP regulations and keep their products safe for the trial subjects.

(Response) We are not issuing the companion guidance in place of minimum CGMP requirements. CGMP is required by statute, and the companion guidance provides our current thinking on complying with statutory CGMP. As previously stated, this action is

intended to focus a manufacturer's effort on applying CGMP that is appropriate and meaningful for phase 1 investigational drugs, and to streamline and promote the drug development process while ensuring the safety and quality of the earliest stage investigational drug products. We also expect this action to help promote innovative, simple, and inexpensive approaches to complying with the statutory CGMP requirements. As discussed in our response to comment 13, we are willing to discuss with the manufacturer alternative approaches that comply with the statutory requirements and that may be more innovative, simple, or inexpensive than the recommendations in the companion guidance.

(Comment 22) Several comments express concern that guidance is not legally binding and therefore, not enforceable. One of the comments states that relying on guidance invites misunderstandings and inconsistencies, while another comment believes that if not required under part 211, manufacturers may not take the time to read or familiarize themselves with guidance related to CGMP, i.e., testing, manufacturing sterile or aseptic dosage forms, and employee qualification/training. A comment also believes that guidances do not undergo the same level of notice and comment, and lacks the complete input of interested parties.

(Response) We agree with the comment that the companion guidance is not legally binding and not enforceable. However, the statutory requirement that drugs, including investigational drugs for use in phase 1 trials, comply with CGMP is legally binding and enforceable. We believe that a sponsor, guided by its knowledge, experience, and technical information applying good scientific methodology, following FDA recommendations, and undertaking appropriate activities (e.g., training), can adequately and appropriately comply with statutory CGMP. We disagree that relying on guidance invites misunderstandings and inconsistencies. In fact, to the contrary, we believe that guidance reduces misunderstandings and inconsistencies because guidance provides FDA's interpretation of or policy on a regulatory issue, while still allowing for flexibility and innovation.

With regard to adequate notice to, and comment by, interested parties on guidance documents, the public can participate in the development and issuance of guidance documents as described in § 10.115(f) and (g), i.e., provide comment on issued draft guidance documents, suggest areas for guidance document development, submit drafts of proposed guidance documents for FDA to consider, suggest that FDA revise or withdraw an already existing guidance document, or comment on FDA's annually published list of possible topics for future guidance document development or revision. Therefore, we disagree with the comment that guidance does not undergo sufficient notice and comment, and lacks the complete input of interested parties. Moreover, we received extensive comments on the draft companion guidance from numerous entities and have considered these comments in preparing the companion guidance.

(Comment 23) Two comments express concern regarding the effect of the companion guidance on the 1991 guidance on preparation of INDs, which recommends the application of certain sections of parts 210 and 211 to phase 2 and phase 3 clinical trials. The comments also request that FDA clarify the status of the 1991 guidance for phase 2 and phase 3 materials with regard to complying with CGMP requirements. Another comment asks if FDA expects an incremental application of CGMP for the production and testing of phase 2 and phase 3 clinical supplies, or if the 1991 guidance will remain in effect for phase 2 and phase 3 materials until the new phase 2 and phase 3 guidance document is available.

(Response) As stated in the introduction of the companion guidance, the companion guidance will replace the 1991 guidance only as it applies to phase 1 investigational drugs. This action does not affect the scope of the 1991 guidance as it applies to phase 2 and phase 3 investigational drugs, which remains in effect until superseded by a subsequent guidance document.

(Comment 24) One comment states that the guidance would allow the same person manufacturing the material (a non-QC unit employee) to also release the material to the clinic. The comment further states that the release of material by a non-member of the QC unit violates United States CGMP and a non-Qualified Person violates European Union CGMP, and does not appear to recognize the importance of having an experienced and knowledgeable unit or person to safely release the materials.

(Response) We agree with this comment in part. The companion guidance recognizes the need to have quality control in this early phase of clinical trial material manufacture and has provided recommendations for the quality control procedures that should be used. We provide flexibility for operations where a very small amount of clinical material is produced. While we agree that release of material by an untrained person violates United States CGMP, this is not what is recommended in the companion guidance, which indicates that, under very limited circumstances and where justified, only a person trained in CGMP and quality control functions should be given the dual responsibility of manufacture and release. The interpretation in the companion guidance is consistent with the quality unit functions under part 211 and the nature of commercial and investigational products.

H. Impact

(Comment 25) FDA makes the following statement in the direct final rule (71 FR 2458 at 2461). ''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.'' Two comments state that because it is unknown at the time of clinical manufacture if a phase 1 drug will continue to phase 2, manufacturers will likely elect to take a conservative approach and manufacture a drug to phase 2 requirements (part 211) to allow the phase 1 drug to be used in future phase 2 studies. Because of availability concerns in the clinical phase, manufacturers would most likely elect to not discard phase 1 material that could be used in phase 2. Therefore, the statement regarding savings is questionable.

(Response) We agree with the comment that some manufacturers may decide to follow part 211 when manufacturing phase 1 investigational drugs. However, the saving estimate was intended to be an estimate of incremental savings should manufacturers chose to follow the companion guidance, as some manufacturers will.

(Comment 26) One comment requests that FDA evaluate the cost of compliance against the hypothetical public health risk of a product that did not reach the market and the likelihood and severity of risks to volunteers. Another comment states that the additional risk to patients in a phase 1 clinical trial does not justify the proposed savings of $1,440 per IND in documentation, training, and other ''reduced'' requirements. The comment also states that the potential costs of $810 per IND is a gross underestimation

of how much it will cost to manufacture a sterile or aseptic product for the first time.

(Response) In section V.F of this document, the responses to comments 16 through 20 state that there will be no change in the risk to patients in phase 1 clinical trials as a result of the final rule. The cost estimate was intended to capture the incremental cost of complying with the proposed rule given current practice under part 211; it does not reflect total costs. A cost-benefit analysis of phase 1 clinical trials or clinical trials in general is beyond the scope of this document.

(Comment 27) One comment believes that the expense is not for compliance with CGMP, especially if systems and procedures are simple, but for the training of personnel.

(Response) Training personnel is a cost of complying with the current CGMP regulation; the estimate in the proposed rule captured the incremental increase in training costs to comply with the proposed rule.

VI. Analysis of Impacts

FDA has examined the impacts of this 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 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 clinical trials from compliance with specific regulatory requirements does not add to the compliance burden of small entities, and in most cases reduces it, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

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 $127 million, using the most current (2006) 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 final rule is to amend our current CGMP regulations to exempt the manufacture of investigational drugs used in phase 1 clinical trials from compliance with the requirements in part 211. The rule affects 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 in-house investigational drugs for use in phase 1 clinical trials and also produce approved drug products for marketing, this final rule is expected to reduce the amount of documentation they produce and maintain when they manufacture an investigational drug for use in a phase 1 clinical trial. In some cases, it should also reduce the amount of component and product testing.

Because they currently may not supply the pharmaceutical industry, some chemical manufacturers and laboratories may experience a slight increase in documentation if they 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 manufacturing 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 compliance with the statutory CGMPs that are necessary in the manufacture of investigational drugs used in phase 1 clinical trials, and to exempt certain drugs produced under IND and used for phase 1 clinical trials from regulatory CGMP requirements under part 211. Some manufacturers may realize savings because they no longer must meet certain requirements. The savings to drug manufacturers that manufacture in-house the investigational drugs used in phase 1 clinical trials will vary greatly from product to product. FDA lacks data to estimate where the cost savings will occur in the manufacture of investigational drugs. Some substantial savings may be realized in 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 manufacture in-house investigational drugs used in phase 1 clinical trials could potentially save between 24 to 40 hours per IND[2]. In addition, the clarifications we have made could lead some large firms to produce in-house future investigational drugs for use in phase 1 clinical trials, rather than contracting the work out.

For previously described 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 manufactured. 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.[3]

The facility that manufactures the investigational drugs used in phase 1 clinical 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.

We receive an average of 1,410 INDs each year.[4] However, this rule would not apply to the majority of these INDs because they are for drug products that already have premarket 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

[2] Eastern Research Group (1195), *Economic Threshold and Regulatory Flexibility Assessment of Proposed Changes to the Current Good Manufacturing Practice Regulations for Manufacturing, Processing, Packing, or Holding Drugs (21 CFR 210 and 211)*, submitted to the Office of Planning and Evaluation, FDA. Estimated hours to change minor and major SOPs for large establishments (p. 24, table 7).

[3] Eastern Research Group (1995), ibid., Estimated hours to change SOPs for small establishments.

[4] The annual number of INDs received varies from year to year; 1,410 is the mean of the total number of research and commercial INDs received by the Center for Drug Evaluation and Research and CBER between 2001 and 2005.

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 1,410, this rule would affect about 425 INDs per year. A firm may produce multiple drug products for phase 1 clinical trials in a given year and use different companies to manufacture 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 investigational drugs used in phase 1 clinical 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 manufacturing in-house, assuming a time savings of 32 hours per application, a fully loaded wage rate of $46, [5] and 150 INDs per year (approximately 35 percent of 425) would total $220,800 per year or $1,472 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 $46, and 275 INDs (approximately 65 percent of 425) affected per year, would total $227,700 per year or $828 per IND.

Although we do not know the number and size distribution of the entities affected by this rule, the impact on them will be negligible and should actually reduce the compliance burden for some. Manufacturers of drug products for phase 1 clinical trials are currently required to manufacturer them using CGMP, but some of the requirements in part 211 are not applicable for the manufacture of small quantities used in phase 1 clinical trials. While exempting these products from part 211, the companion guidance clarifies FDA's thinking on how to manufacture phase 1 investigational drugs under CGMP and does not include recommendations that would increase the burden of compliance.

[5] Bureau of Labor Statistics, *National Compensation Survey*, 2005. Wage rate is the average of the hourly rate for postsecondary chemistry teachers ($38.82) and postsecondary biochemistry teachers ($27.01) plus 40 percent to account for benefits and rounded to the nearest whole dollar, *www.bls.gov*, data accessed September 2006.

VII. Paperwork Reduction Act of 1995

This 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 final rule, the production of human drug products, including biological drug products, intended for use in phase 1 clinical trials are exempted from complying with the requirements under part 211. Part 211 contains information collection requirements that are approved by OMB under control number 0910–0139. As explained in the following paragraph, the information collection requirements in part 211 are reduced in this final rule.

The OMB-approved hourly burden to comply with the information collection requirements in part 211 (OMB control number 0910–0139) is 848,625 hours. FDA estimates that, under the final rule, approximately 425 investigational drugs are exempted from complying with the requirements under part 211. Based on this number and the total number of drugs that are subject to part 211 (122,795), FDA estimates that the burden hours approved under OMB control number 0910–0139 will be reduced by approximately 2,936 hours (425/122,795 x 848,625). Thus, as a result of the final rule, the amended burden hours in OMB control number 0910–0139 are approximately 845,689 hours.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that 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.

IX. Federalism

FDA has analyzed this 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.

X. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. Wood, A.J.J., J. Darbyshire, ''Injury to Research Volunteers—The Clinical-Research Nightmare,'' *The New England Journal of Medicine*, 354:1869–1871, 2006.

2. Steinbrook, R., ''Protecting Research Subjects—The Crisis at Johns Hopkins,'' *The New England Journal of Medicine*, 346:716–720, 2002.

3. Savulescu, J., ''Harm, Ethics Committees and the Gene Therapy Death,'' *The Journal of Medical Ethics*, 27:148–150, 2001.

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, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 2. In § 210.2, add 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 described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 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 described 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 phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

Dated: July 9, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–16011 Filed 7–14–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

28 CFR Part 0

[Docket No. DEA–310F]

Redelegation of Functions

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: This rule makes one revision to the Drug Enforcement Administration's (DEA) regulations concerning agency management. Additional personnel are authorized to sign and issue administrative subpoenas.

DATES: *Effective Date:* July 15, 2008.

FOR FURTHER INFORMATION CONTACT: Wendy H. Goggin, Chief Counsel, Drug Enforcement Administration, 8701 Morrissette Drive, Springfield, VA 22152, Telephone (202) 307–1000.

SUPPLEMENTARY INFORMATION: This Final Rule implements one change to Title 28, Code of Federal Regulations (CFR), Part 0 by adding three officials to the list of officials who may sign and issue administrative subpoenas pursuant to the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91–513, 84 Stat. 1236 (1970), as amended (the Act), codified at 21 U.S.C. 801–971. In addition to the Attorney General and the DEA Administrator, the current list of such officials is set forth at 28 CFR, Chapter I, part 0, Appendix to Subpart R, Section 4. Title 21, U.S.C. 875 and 876, provide the authority to issue such subpoenas. By 28 CFR 0.100, the Attorney General has delegated this authority to issue administrative subpoenas in support of his functions and duties under the Act to the DEA Administrator. The DEA Administrator is permitted by 28 CFR 0.104 to redelegate this authority ''to any of [her] subordinates[.]''

By this Final Rule, DEA now extends this administrative subpoena authority to its senior officials overseas who often supervise investigations with leads back in the United States, *i.e.*, DEA's Regional Directors, Assistant Regional Directors, and Country Attachés. As Title 28 CFR, Chapter I, Part 0, Appendix to Subpart R, Section 4 is presently written, DEA Resident Agents in Charge and Special Agent Group Supervisors posted outside the United States have such authority while their superiors, *i.e.*, Regional Directors, Assistant Regional Directors, and Country Attachés, do not. The amendment to section 4 is designed, in part, to rectify this anomaly.

Title 28 CFR, Chapter I, Part 0, Appendix to Subpart R, Section 4 currently lists twelve categories of DEA and FBI officials who are empowered to sign and issue administrative subpoenas under 21 U.S.C. 875 and 876. To this list of senior officials DEA now adds its Regional Directors, Assistant Regional Directors, and Country Attachés. This is being done to rectify an oversight. While both DEA Resident Agents in Charge and Special Agent Group Supervisors posted outside the U.S. have authority to sign and issue such administrative subpoenas, unlike the case of Resident Agents in Charge and Special Agent Group Supervisors within the U.S., the superior officials (Regional Directors, Assistant Regional Directors, and Country Attachés) of such Resident Agents in Charge and Group Supervisors serving overseas have not heretofore been listed at Title 28 CFR, Chapter I, Part 0, Appendix to Subpart R, Section 4, as officials to whom the Administrator has redelegated her authority to sign and issue administrative subpoenas.

Regulatory Certifications

Administrative Procedure Act

This rule relates to a matter of agency management or personnel and is a rule of agency organization, procedure, and practice. As such, this rule is exempt from the usual requirements of prior notice and comment and a 30-day delay in effective date. *See* 5 U.S.C. 553(a)(2), (b)(3)(A), (d)(3).

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601–612, has reviewed this rule, and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities because it pertains to personnel and administrative matters affecting the Drug Enforcement Administration. Further, a Regulatory Flexibility Analysis was not required to be prepared for this final rule because the Drug Enforcement Administration was not required to publish a general notice of proposed rulemaking for this matter.

Executive Order 12866

This rule has been drafted and reviewed in accordance with Executive Order 12866, Regulatory Planning and Review, section 1(b), Principles of Regulation. This rule is limited to agency organization, management and personnel as described by Executive Order 12866 section (3)(d)(3) and, therefore, is not a ''regulation'' or ''rule'' as defined by that Executive Order. Accordingly, this rule has not been reviewed by the Office of Management and Budget.

Executive Order 12988

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988, Civil Justice Reform.

Executive Order 13132

This rule will not 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. Therefore, in accordance with Executive Order 13132, Federalism, the Drug Enforcement Administration has determined that this rule does not have sufficient federalism implications to warrant the preparation of a federalism summary impact statement.

Unfunded Mandates Reform Act of 1995

This rule will not result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $120 million or more (adjusted for inflation) in any one year, and it will not significantly or uniquely affect small governments. Therefore, no actions are necessary under the provisions of the Unfunded Mandates