

GMP and Phase 1 Clinical Trials: Streamlining the Critical Path?

Gordon B. Richman

FDA is modernizing and streamlining the regulatory processes for medical product development. This article examines FDA's proposed rule to exempt the production of Phase 1 clinical trial materials from the GMP regulations and questions whether this proposed exemption will truly improve public health and promote faster and more predictable access to new medicines.

FDA has expressed its commitment to modernize the pharmaceutical good manufacturing practice (GMP) regulations by 2010 and to streamline the clinical development process to “ensure that basic scientific discoveries translate more rapidly into new and better medical treatments” (1–2). On January 17, 2006, the agency took its first significant step toward its streamlining goal and issued a proposed rule that seeks to exempt the manufacture of most investigational new drugs and biologics used in Phase 1 clinical trials from compliance with the GMP regulations (3). FDA also published a draft guidance document to outline “specific standards for the manufacture of small amounts of drug product for Phase 1 studies” and “an approach to cGMP compliance that is appropriate for the particular stage of drug development” (1, 4).

Most commentators welcomed FDA's proposal and expressed firm support for increasing regulatory flexibility, reducing the GMP compliance burden during clinical development, and facilitating a faster route to these early human studies. But the agency also has received stern criticism and serious questions about the scientific evidence for its position and the increased risk to Phase 1 trial subjects that might result from drugs being manufactured outside the scope and reach of the GMP regulations. This article examines the proposed rule and draft guidance to assess whether this first streamlining step will meet the stated goals and truly move us down the critical path toward better product development.

Investigational new drugs and GMP

The current debate and FDA–industry discussions are nothing new. In fact, the agency first addressed this issue nearly 30 years ago, when it publicly rejected the suggestion that the GMP regulations should not apply to the production of investigational products (5). FDA and the regulated industries have recognized that most early-phase studies are conducted long before the details of the product formulation,

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manufacturing specifications, and production process have been fully defined and that some of the GMP requirements simply are not logically applicable to Phase 1 development circumstances. So, time has not served to quiet the debate, and there continue to be widely divergent views on exactly how the rules should be applied during early clinical development.

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 . . . [and e]ven though the chemicals from which the placebos are made are not intended to

ucts. Accordingly, FDA is committed to ensuring that investigational drug products are manufactured using adequate manufacturing facilities to ensure good quality control” (emphasis added) (6).

FDA’s recent proposal and draft guidance now seek to change this longstanding position.

FDA’s 2006 proposed rule

In January, FDA issued a direct final rule and a companion proposed rule to exempt most Phase 1 study drugs from the GMP regulations, along with a draft guidance document that provides more details about the agency’s manufacturing practice expectations (3, 7, 8). The agency’s stated goal is to “streamline and promote the drug development process while ensuring the safety and quality of the earliest stage investigational drug products” (7). The agency later withdrew the direct final rule because of “significant adverse comments,” which resulted in FDA’s automatically reverting back to the proposed rule as the basis for its intended actions (8). So until the agency issues a new final rule, the GMP regulations remain in full force and in effect for Phase 1 study drugs, and it is not at all clear whether FDA intends to apply the interpretations outlined in the draft guidance in the meantime.

FDA has stated that its proposal 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” (7). Under this “appropriateness” standard, instead of relying on the regulations, FDA would continue to “exercise oversight of production of these drugs under the agency’s general statutory CGMP authority and investigational new drug (IND) authority” (3). So even though FDA is proposing to exempt most Phase 1 materials from the GMP regulations, the agency will still expect producers to conform to “current good manufacturing practices” as required under the law—specifically, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). In addition, the exemption that FDA “giveth” the agency will then “taketh” away: if the “investigational

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FDA’s previous position

Since the late 1970s, FDA has stood firmly by its position that the GMP regulations apply in full to clinical trial materials, throughout all phases of development. The agency was clear and consistent in several public statements on the issue and left little question about its views on the importance of ensuring the quality and integrity of drugs and biologics that were intended for use in human clinical studies.

In September 1978, FDA sternly rejected comments that urged the agency to exempt investigational drugs and biologics (as well as placebos) from the application of the rules. FDA’s views were based on the premise that the quality and integrity of clinical trial materials were critical to both the proper conduct of human studies and the scientific foundation for further clinical trials. The agency very clearly stated its position that the “GMP regulations apply to the preparation of any drug product for administration to humans or animals,

cause a direct pharmacologic response, the maintenance of their quality is [also] important because of their use in patients, particularly in controlled drug studies” (emphasis added) (5).

In its 1991 *Guideline on the Preparation of Investigational New Drug Products*, FDA further elaborated its position and expressed a clear recognition that the body of available manufacturing information, specifications, and controls will advance during development but may be very limited in early clinical phases. The agency, however, reiterated its firm commitment to apply the GMP requirements and ensure compliance throughout all phases of development: “FDA, while recognizing the differences between the manufacture of investigational products and commercial products, believes that *it is nonetheless vital that investigational products be made in conformance with current good manufacturing practice . . . Product safety, quality, and uniformity are especially significant in the case of investigational prod-*

drug has already been manufactured . . . for use during Phase 2 or Phase 3 studies or has been lawfully marketed, [the] manufacture of such a drug must comply with the appropriate sections of 21 *CFR* Part 211 for the drug to be used in any subsequent Phase 1 investigational studies, irrespective of the trial size or duration of dosing” (4).

In describing the statutory GMP standard it intends to apply to the production of Phase 1 products, FDA refers to the language in the law that defines a drug as “adulterated” (and therefore illegal to manufacture, ship, or receive) 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 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” (7).

So, what does FDA believe will be sufficient to meet this legislative standard? On that point, the agency is recommending that producers of Phase 1 drugs implement the basic manufacturing controls and quality-system principles outlined in the draft guidance document. Because the applicability of the draft guidance remains unclear in the wake of FDA’s withdrawal of the direct final rule, manufacturers should continue to comply with the existing requirements of the regulations.

January 2006 draft guidance: an overview

FDA’s draft guidance document outlines a broad range of manufacturing and quality-related recommendations for producing Phase 1 clinical trial materials. The recommendations are “designed to provide approaches to CGMP that appropriately address factors associated with the production of clinical supplies” and “an appropriate quality framework” that can be used “to comply with the requirements” of the statute (4). FDA intends to use a finalized version of the guidance to replace the 1991 guideline for Phase 1 drugs

Draft guidance recommendations

The draft recommendations cover personnel qualifications; the QC function (including roles and responsibilities for examining components for conformance to defined quality standards, review and approval of production and testing procedures and acceptance criteria, releasing or rejecting each batch based upon the review of production and testing records, investigating unexpected results or errors, and initiating corrective actions); facilities and equipment; procedural and physical control of components; production procedures and documentation; laboratory controls for analytical testing and stability studies; container closure and labeling; handling and transport of the study drug; and the maintenance of “complete records related to the quality and operation of the production processes” (4).

(*i.e.*, leaving the guideline in place for Phase 2 and Phase 3 studies).

The draft recommendations are based upon FDA’s stated belief “that applying quality control (QC) principles to the production of investigational products (*i.e.*, interpreting and implementing CGMPs consistent with good scientific methodology)” will both facilitate the conduct of early phase trials “and protect study subjects” (4). The agency also believes that product quality control during Phase 1 development is achieved primarily by having “[w]ritten procedures that are well defined . . . [e]quipment that is adequately controlled . . . and [d]ata from production, including testing, that are accurately and consistently recorded” (4).

Based upon this fundamental quality philosophy, the draft guidance describes approaches and good practice expectations that cover many of the same basic GMP topics that are already addressed in the existing regulations (see sidebar, “Draft guidance recommendations”).

The guidance document also reflects FDA’s current thinking with regard to quality systems and risk management (more appropriately described as “hazard control”) principles, consistent with the agency’s ongoing “CGMPs for the 21st Century” initiative. For example, FDA recommends that producers of Phase 1 study drugs conduct a “formal evaluation of the production environment to identify potential hazards” and carefully consider risks “that might adversely affect the resulting quality of [the] investigational product” (4). These hazard control analyses should then result in “appropriate actions prior to and during production to minimize

risks and safeguard the quality of the investigational product,” including the establishment of “production controls based on a risk assessment for the product and manufacturing process and [that] follow good scientific and quality control principles” (4).

Comments and analysis

As noted previously, most of the comments on the proposed rule and draft guidance have been generally supportive of the agency’s actions. But they also include numerous requests for further clarification, along with very serious criticism and challenges concerning the evidence that FDA is relying on to support the proposed exemption and its analysis of the estimated benefits and potential risks. Even the very supportive comments from the regulated industries have highlighted concerns about inconsistencies between the proposal, the stated expectations established in Europe, and some of the basic quality systems concepts that FDA is recommending under the 21st century GMP initiative.

In their current forms, the proposed rule and draft guidance appear to raise more questions and open more issues that they seek to resolve, and certainly more than can be fully addressed in this article. The following are selected examples of some of the most important concerns.

Safety and complexity

FDA has acknowledged that “[b]ecause safety issues are a significant cause of delay and failure during development, some have advocated simply lowering safety standards” to allow for better screening of compounds in early clinical

studies (10). The agency, however, emphasized that “[f]or ethical human testing, there is wide agreement that reasonable assurance of safety must be achieved before clinical trials begin” (10). It is unclear how FDA’s current proposal would provide this reasonable assurance of safety-first.

The proposed exemption would apply to an extremely complex range of Phase 1 products that have widely varying and often even more complex risk-benefit profiles. FDA intends the scope of the exemption to include “investigational new human drug and biological products (including finished dosage forms used as placebos) intended for human use during Phase 1 development, including, for example, investigational recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, *in vivo* diagnostics, plasma derivative products, blood and blood components, gene therapy products, and somatic cellular therapy products (including xenotransplantation products)” (4).

FDA also implies that the same approach could be extended beyond finished dosage forms and that producers of “new active pharmaceutical ingredients . . . should implement controls appropriate to the stage of development and, thus, may want to consider the recommendations described in this guidance” (4). In the face of these product and therapeutic complexities, FDA does not draw any distinctions or stratify the proposed exemption. It is difficult to understand, or even envision, the agency’s scientific rationale for a blanket exemption that would fully remove all of the listed Phase 1 materials from the reach of the GMP regulations.

Some of the most pointed criticism submitted to FDA focused heavily on the logical relationship between GMP compliance and clinical safety. In an April 3, 2006 letter to the agency, Public Citizen’s Health Research Group strenuously objected to the proposal, stating: “The reason we have GMPs is because manufacturing drugs is a difficult task best not left to amateurs . . . Without evidence, it is claimed that having to actually produce drug or biological

products according to accepted international standards is a barrier too high for entry into Phase I studies. But all barriers do (or at least should) serve a social purpose—in this case, preventing those incapable of following or unwilling to follow GMPs from administering investigational products to humans . . . We can see no reason why subjects in Phase I clinical trials should be any less deserving of FDA protection than those in later phases of development (or, subsequently, marketing) . . . Healthy volunteers and patients with advanced diseases place their bodies on the line in Phase I studies, hoping to improve medical outcomes for future generations. The least they deserve is a properly manufactured drug” (11).

“reasonable assurance of safety” for Phase 1 clinical trials to proceed.

A robust, efficient, and predictable development pathway?

According to FDA, biomedical science and improvements to the development process must be based on “the explicit goal of robust development pathways that are efficient and predictable and result in products that are safe, effective, and available to patients” (10). The agency’s proposal, however, creates more uncertainty and thus does not appear to advance the process toward a more robust, efficient, or predictable path.

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Public Citizen also noted the highly publicized safety problems encountered in a recent Phase I study in the United Kingdom and the importance that GMP compliance played in identifying the root cause of the adverse reactions: “The recent disaster with TGN1412, in which six healthy Phase I volunteers had to be placed on ventilators, some comatose, may not seem [directly] relevant to this FDA proposal. But in Britain, which has not sought to absolve drugs for Phase I trials of the requirements to comply with GMPs, there is some assurance that the problems observed are not due to production problems, but rather are intrinsic to the product being tested. Having some degree of confidence that a drug is properly manufactured helps greatly in the investigation of such incidents” (11).

It will be interesting, to say the least, to see how FDA addresses these safety and complexity concerns to achieve the

tions and nearly three decades of good practice interpretations reflected in agency policies and inspectional observations. In place of this familiar GMP body of knowledge, FDA’s draft guidance recommends the application of essentially the same scientific principles that are embedded in the regulations themselves. This hardly appears to simplify matters.

If the agency finalizes the proposed rule without significant changes, FDA would exchange the existing, more developed GMP standards in the regulations for an unenforceable, nonspecific guidance document that provides far less clarity, and that will require more interpretation of broadly stated concepts by the same individuals and firms that struggle to properly apply the current requirements. The following are just a few examples of the subjective and open-ended language in the draft guid-

ance that will only increase the potential for more confusion and debate (emphasis added):

- “interpreting and implementing CGMPs consistent with good scientific methodology;”
- “establish production controls based on a risk assessment for the product and manufacturing process and follow good scientific and quality control principles,” taking into account “risks from the production environment that might adversely affect the resulting quality of an investigational product;”
- “appropriate actions prior to and during production to minimize risks and safeguard the quality of the investigational product.”

The draft guidance takes another big step toward uncertainty by suggesting that the traditional requirement for independent quality oversight and review—one of the most important fundamental concepts of both GMP and quality systems—might not fully apply in certain circumstances: “We also recommend that QC responsibilities be performed independently from production responsibilities . . . However, in limited circumstances, depending on the size and structure of an organization, all QC functions could be performed by the same individual. For example, in some small operations, it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch. Under such circumstances, we recommend that another qualified individual not involved in the production operation carry out an additional, periodic review of production records” (4).

This circumstantial suspension of the absolute need for quality independence also raises questions about what FDA intends the following vague and undefined terms to mean (emphasis added):

- “in *limited circumstances*, depending on the size and structure of an organization” “in some *small operations*;”
- “another qualified individual not involved in the production operation” (which is difficult to envision if the firm doesn’t have sufficient resources for a production-independent quality review as part of its routine operations);

- “additional, *periodic* review of *production records*” (which doesn’t even suggest a range of acceptable frequency and possibly implies that the traditional notion of a batch record may no longer apply);
- the additional production record review is ambiguously recommended to be performed at some undefined time in the process (*i.e.*, before, during, or after the release of the product).

In light of these uncertainties, it is especially difficult to understand how FDA believes that small operations and research-based laboratories—that is, those relatively GMP-inexperienced producers that view the existing regulations as an overly burdensome impediment—will be any better equipped to meet the basic quality system and hazard control principles outlined in the guidance.

Ensuring Phase 1 IND and GMP compliance

The proposed rule suggests that FDA will still have sufficient authority to effectively enforce the GMP requirements, based on the language of the statute and its regulatory oversight of the IND process and inspections. The agency has described the regulatory powers that it will continue to apply to the production of Phase 1 drugs as follows: “FDA reviews the submitted information [in an IND application] to determine whether the drug to be used in the investigational study has the identity, quality, purity, strength, and potency necessary to ensure the safety of subjects in the proposed Phase 1 study. In certain circumstances, the Agency may choose to conduct an inspection (*e.g.*, if there is insufficient information to assess the risks to subjects or if the subjects would be exposed to unreasonable and significant risk). Alternatively, the Agency could decide to place a proposed or ongoing Phase 1 investigation on clinical hold or terminate the IND. Such actions can also be taken if there is evidence of inadequate quality control procedures that would compromise the safety of an investigational product” (4).

FDA’s traditional exercise of enforcement discretion is based upon its authority and ability to make these kinds

of subjective decisions, so the agency’s description of its oversight and potential options during Phase 1 does not reflect anything out of the ordinary. Because the draft guidance is intended to outline how FDA will continue to interpret the statutory GMP requirement, the industry is likely to look to the agency’s language to further define the boundaries and enforcement guide-rails that will remain. This raises several predictable questions and areas of uncertainty.

For example, how would FDA know or determine that “there is evidence of inadequate quality control procedures that would compromise the safety of an investigational product”? Given the limited level of detail ordinarily included in the chemistry, manufacturing, and controls section of an IND, it seems unlikely that FDA would have sufficient information to identify this “evidence” in the application itself. How would FDA make this determination? After the product’s safety was compromised and it was manifested in a Phase 1 subject being harmed? Based on the regulatory history at the site or firm?

The agency also stated that it could “choose to conduct an inspection . . . if there is insufficient information to assess the risks to subjects or if the subjects would be exposed to unreasonable and significant risk.” This also is difficult to imagine as a practical matter. During the past few years, FDA has repeatedly expressed its limitations in terms of inspectional resources. Indeed, this is a key factor in the agency’s efforts to implement a risk-based mechanism for assessing its inspectional priorities. In addition, for a very long time, FDA has not even had enough resources to meet its statutory requirement to conduct routine biennial GMP inspections, especially in the case of foreign manufacturing facilities. Based on the agency’s existing resource constraints, it is nearly impossible to imagine that FDA would choose to conduct a Phase 1 GMP inspection, except in response to a catastrophic safety problem. Although FDA could certainly take enforcement action against the manufacturer, it would be too late to protect the clinical study subjects.

Recent public criticism also raises questions about the agency's reliance on its existing oversight of clinical trials as an adequate GMP compliance safety net. In just the last year, FDA has been the target of stern criticism from Congress regarding its regulatory oversight of clinical trials, informed consent, emergency research, institutional review boards, and the safety of study subjects. Public reports have also included statements from existing and former FDA officials that seriously question the agency's ability to monitor the conduct of trials and its record on enforcing the rules. For example, a November 2, 2005 article included the following points that clearly undermine the agency's position on its clinical oversight: "FDA's chief clinical trial regulator for investigational drugs says much more oversight is needed in clinical trial programs and the agency doesn't have enough staff to aggressively monitor them. In an 11/2 *Bloomberg News* exposé on clinical trials and lax monitoring by IRBs, conflicts-of-interest, and poor regulatory oversight by FDA, CDER's Division of Scientific Investigations director Joanne Rhoads said the agency's inspection process alone cannot maintain quality in clinical trials. . . . 'FDA's own enforcement records portray a system of regulation so porous that it has allowed rogue clinicians—some of whom have phony credentials—to continue conducting human drug tests for years, sometimes for decades,' the *Bloomberg* article charges. . . . Former FDA investigator and now-consultant Michael Hensley says the agency has become less active in clinical trial oversight in recent years. 'The FDA's backbone has been Jell-O,' he says. 'The folks at the FDA stopped enforcing the rules several years ago'" (12).

Members of Congress and other observers will certainly be interested to see how FDA addresses these practical oversight and enforcement issues in the next step of the rulemaking process.

Conclusion

FDA is to be commended for working toward the laudable goal of advancing public health by improving the product-development process and increasing the

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speed and likelihood of new and better medical treatments being made available. There is wide agreement among the interested parties that we need to take informed scientific steps toward solutions that have significant potential to advance the cause and at the same time minimize any increased risks to clinical trial subjects. Although there is no perfectly predictable, completely risk-free way forward, the agency needs to go back to the drawing board and develop a more thorough scientific foundation for its proposal and a better balance of potential benefits and risks.

To effectively advance the shared interests of researchers, regulators, clinical trial subjects, academic institutions, and the industry, FDA does not need to completely replace the basic, well-established language of the regulations with less-defined, open-ended, and unenforceable guidance interpretations of the limited GMP language that Congress included in the law. The agency could take a far less controversial step in the right direction by exempting the production of Phase 1 study drugs from the specific sections of the regulations that simply don't logically apply during early development. By taking this more rational first step, FDA could work on developing a more sound scientific approach and, in the meantime, eliminate a significant part of the perceived development impediment.

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