

March 20, 2006

Docket 2005D-0286
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA's draft guidance, *INDs – Approaches to Complying with CGMP During Phase 1*

Dear Members of the U.S. Food and Drug Administration,

Thank you for the opportunity to comment on the agency's recent draft guidance. I am very concerned about FDA's proposal to exempt phase 1 material from the CGMP regulation, and to replace the existing regulation with a guidance document. This proposal is ill-advised, and would put patients in phase 1 at great risk. My comments on (or objections to) the draft guidance follow.

- Not legally binding** The guidance is not legally binding, nor is anyone required to follow it. The guidance makes *recommendations* rather than stating requirements. Individuals producing materials for human use should be required to follow a regulation. Anyone who does not have sufficient, trained and experienced staff, and the necessary facilities and equipment, should not be manufacturing material for human use. If the agency wishes to pursue this approach, the draft guidance and comments received could be used as the start of a proposed CGMP regulation for investigational materials, as the agency had always considered doing.
- Non QC Unit personnel may release product** The guidance allows a non-QC unit employee to release material, and the same person who manufactured the material to release it. This is a clear violation of U.S. current good manufacturing practice, and it demonstrates a lack of understanding of the benefit of having experienced quality assurance personnel. It is also a violation of the European Union CGMPs, which require that a Qualified Person (QP) release clinical and commercial product. Even pharmacists learn that when compounding sterile or aseptic product, they must incorporate necessary checks and balances.
- Unethical** Allowing the production of *some* phase 1 materials to be made to a lesser standard than that used for materials in phase 2 or 3 trials, or for commercial production, is a violation of the ethical principles for the protection of human subjects in research, as stated in the Belmont Report and the Declaration of Helsinki. The Belmont Report states that "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly... Another way of conceiving the principle of justice is that equals ought to be treated equally." The Declaration of Helsinki states that "In research on man, the interest of science and society should never take precedence

over considerations related to the well-being of the subject." In addition, the FDA has detailed regulations concerning preclinical (or animal) testing (21 CFR 58), which require a Quality Assurance Unit. With this proposal, FDA is continuing to require following CGMP regulations for phases 2 and 3. Questions: Are patients and volunteers in phase 1 less valuable than an animal? Are patients in phase 1 less valuable than patients in phases 2 and 3? Why drop the protection of the regulation in phase 1?

Insufficient aseptic or sterile information

The guidance currently contains little more than one page on manufacturing sterile or aseptic products, and makes no reference to media fills. Manufacturing sterile or aseptic dosage forms requires a higher level of skill and judgment. The agency's guidance on *Sterile Drug Products Produced by Aseptic Processing* is very detailed and contains 63 pages. It is illogical to assume that a drug manufacturer, chemical manufacturer, or (medical research) laboratory making clinical material for the first time would be able to follow this guidance and make sterile or aseptic materials safely. It is illogical to assume that they would read or become familiar with other FDA guidance documents, or take the time to learn or practice CGMP, without having to do so per CGMP regulation. From a practical point of view, it is extremely difficult to teach aseptic technique, or to learn and practice it, even for experienced laboratory employees.

Insufficient equipment/facility/environmental monitoring controls

The guidance does not yet discuss the equipment and/or facilities that would be needed in order to manufacture sterile or aseptic material safely. The guidance does not currently limit the movement of employees from an animal colony (which may be on site) to the human clinical material production area (this is a CGMP requirement of the European Union GMPs). (I am aware of two biotechnology companies where their lack of limiting this movement caused contamination in their manufacturing facility.) The guidance document allows GMP and non-GMP work to be performed in the same area. Historically, this has caused great difficulty in ensuring that employees follow CGMPs. The guidance document *recommends* that equipment used for sterilization be qualified, even though sterilization is a critical operation, and some smaller organizations may attempt to use (or be using) the same autoclave to sterilize both animal and human glassware.

Insufficient testing requirements

The guidance document *strongly recommends* performing confirmatory identity testing on active pharmaceutical ingredients, but it does not require it. This is a violation of current, good manufacturing practice. As you recall, in the sulfanilamide tragedy that occurred in the 1930s in the United States, diethylene glycol (the equivalent of antifreeze) was used in manufacturing an “elixir” of sulfanilamide, without sufficient testing or controls, and resulting in the death of more than 100 patients. The guidance *recommends* (but does not require) that testing of biological/biotechnological products be done for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, viral clearance or inactivation, and clearance of antibiotics. The guidance document *recommends* (but does not require) that laboratory testing of the investigational product be performed “as appropriate to evaluate identity, strength, potency, purity, and quality attributes.”

Insufficient employee training requirements

The direct final rule states that even though the agency does not know how many entities would be affected by the rule, that they believe that “all of the entities affected by this rule have personnel with skills necessary to comply with requirements.” This is illogical. The amount of training required for aseptic technique alone is substantial, and not yet well described in the guidance.

Lack of understanding of importance of QC unit role

The guidance does not appear to recognize the importance of having an experienced and knowledgeable QC unit (or person) to manufacture the materials safely. The guidance does not yet mention internal or supplier audits (one of the most critical QA functions). The guidance does not yet mention the importance of carefully selecting and continually monitoring any contract facilities used. The guidance does not require approval of proposed changes, but recommends that they be recorded along with the rationale.

Does not demonstrate common sense

In the recent past, we have had several deadly recalls, infant deaths, and blindness associated with drugs compounded by pharmacists. If trained pharmacists are not able to always safely compound products, why would anyone assume that a medical researcher or other employee would be able to make them safely? This approach does not recognize or acknowledge the recent patient deaths in phase 1 safety studies that occurred at the prestigious medical research institutions, Johns Hopkins and the University of Pennsylvania.

From a practical point of view, it has taken years to get industry R&D employees to follow the applicable regulations. History has shown that regulation is needed in order to prevent tragedies from occurring. The U.S. Food and Drug Administration was given inspectional authority because a paper-based review is insufficient. The agency is undermining the QC unit, the one group inside organizations that sets up systems and is responsible for ensuring patient safety and enforcing CGMP requirements.

Proponents of this approach state that ICH Q7A, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, an internationally harmonized guidance, has been used successfully without the need for a regulation. ICH Q7A also has 57 detailed pages, and is used to manufacture material that will be further processed before being delivered to patients. The phase 1 guidance is 17 pages long and provides *recommendations* for drugs and biologics that may be delivered by injection or inhalation, resulting in patient injury or death if the material is improperly prepared or contaminated. FDA also inspects API manufacturers, although they do not routinely inspect in phase 1 unless for cause (or in certain, specified circumstances, such as for Treatment INDs).

Based on assumptions

If data are available, the FDA has provided no data to support their position, such as results or lessons learned from their phase 1 “for cause” inspections, treatment IND inspections, or adverse drug events reported in phase 1. The agency freely admits that it does not keep a database nor know how many entities would be affected by this guidance or rule. What data are the FDA basing this approach on?

I hope that the agency will consider withdrawing the direct final rule and issuing proposed GMPs for investigational drugs and biologics instead. This guidance, once finalized, could be used to provide further clarification or approaches during phase 1, or be used as a start to a proposed rule on CGMPs for investigational materials, but it should not be used to replace an existing regulation.

Sincerely,

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Attachments: 1) A Brief History of the GMPs: The Power of Storytelling article
2) Chipping Away at the GMPs Tutorial (Powerpoint Slides), GMP Conference, University of Georgia (earlier delivered as an audioconference for *BioPharm Magazine*)