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Docket No. 2005N-0285  
Direct Final Rule, 21 CFR 210

and

Docket No. 2005N-0285  
Proposed Rule, 21 CFR 210

In issuing a direct final rule, FDA short-circuited a discussion about the quality of clinical trial material. This discussion is important to establish meaningful, consistent standards that balance patient protection with speed of development. These comments oppose repealing 211<sup>1</sup> for Phase 1 materials. FDA should rescind the direct final rule and engage stakeholders to create a regulation specific to Phase 1 materials that would address the following points.

Furthermore, the discussion in the preamble fails to address important questions about compliance policy and public health. Once the direct final rule is withdrawn, these comments need to be addressed in the proposed final rule.

1. Withdrawing written standards makes the rules impossibly unclear. FDA is not proposing to exempt Phase 1 materials from GMP requirements. Instead, FDA is exempting them from the requirements of 211. FDA will regulate these materials through the general statutory authority. This means that Phase 1 materials will be subject to unwritten standards, developed case-by-case without any input from the public or the industry. This is even more inappropriate when one considers that FDA has minimal experience inspecting Phase 1 materials for compliance with GMP. Individual investigators, District Offices, and review divisions will certainly have differing interpretations. There will be few inspection reports and fewer court cases, so companies will be left without clear rules. Today, inconsistency, non-transparency, and uncertainty slow product development as the industry tries to comply on a shifting landscape of uncertain legal basis; this proposal makes the problem worse.

<sup>1</sup> Throughout, I refer to the Current Good Manufacturing Practice Regulations at 21 CFR §210 and §211 as 211, recognizing that 210 has only definitions and therefore does not establish binding requirements.

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Unclear rules erode quality. Without clear rules, most companies will be responsible and ethical. Some companies, particularly smaller companies, face intense financial pressure on their clinical programs. Many of those companies outsource some or all of the manufacturing to other companies who also face financial pressure. Even ethical people at financially-strapped companies will not be able to justify expenses based on *recommendations* in a *draft* guidance. Inevitably, some companies will stumble, and quality of these company's products will drop.

2. FDA has understated the risk to patients. In the Federal Register, FDA estimates that there are about 255 INDs affected by this change each year, and each of those trials would have no more than 80 patients. That means that the change puts up to 20,400 volunteer subjects at additional risk each year.

Furthermore, FDA has confused two aspects of safety. While rare adverse events related to the pharmacological action of the drug are not typically found in Phase 1, the GMP regulations are designed to protect from gross mishaps. Clinical subjects should be protected from drugs that are contaminated with bacteria, penicillin, or industrial cleaning agents. Clinical subjects should be protected from product mixups; FDA knows that mixups are more likely in manually-labeled small batches. These GMP failures do not cause rare side effects that would not be expected in a small clinical trial. If a person takes a contaminated drug, it is reasonable to think that the person will suffer and perhaps die. If one study article were mixed up with another, the outcome could be catastrophic.

3. FDA provides no evidence that compliance with GMP requirements has hindered development of pharmaceuticals.<sup>2</sup> Clearly, the cost of compliance is a barrier for some companies at Phase 1 just as compliance is a barrier to market entry. This cost must be balanced against other factors. On one hand, there is a financial cost of GMP compliance and a hypothetical public health risk of a product that did not reach the market. On the other hand, there is the likelihood and severity of risks to volunteers. This evaluation is not trivial, but FDA's rule makes no effort to address it. A new proposed rule should evaluate these costs and risks.
4. To cushion the impact of the rule, FDA points to nonexistent patient protections in 21 CFR §312.23, which requires companies to submit information about the clinical material. Submitting general information is no substitute for compliance with GMP. With this reasoning, FDA could repeal the GMP for all products and rely entirely on the information submitted to FDA offices at a considerable cost saving to the government – this reasoning is, of course, absurd. The GMP regulations contain specific requirements that are not redundant to the requirement to file information. The following table contrasts the general requirements for drug products in 312 with those in 211.

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<sup>2</sup> Yet streamlining is the goal of the effort. From the first sentence: "This action is intended to streamline and promote the drug development process ..."

312.23 (in full)	211 (examples only)
<ul style="list-style-type: none"> <li>• Description of the composition, manufacture, and control</li> <li>• Stability data to cover the length of the trial</li> <li>• List of components for the drug product</li> <li>• Name and address</li> <li>• Limits and methods</li> </ul>	<ul style="list-style-type: none"> <li>• Independent quality unit</li> <li>• Trained staff</li> <li>• Adequate facilities, including ventilation and sanitation</li> <li>• Clean equipment</li> <li>• Testing of components</li> <li>• Written records of the manufacturing</li> <li>• Control of microbiological contamination</li> <li>• Control over labeling to prevent mixups</li> <li>• Freedom from contamination with penicillin</li> <li>• Batch record review and release, including resolving deviations during manufacturing</li> <li>• Investigating complaints of product quality</li> </ul>

These requirements in 211 have clear application to the manufacture of clinical supplies, and nothing in 312 addresses them. It is hard to understand how a public health agency would repeal the requirement to investigate and resolve complaints of turbidity or product mix-up.

The requirements in 312.23 are further limited. Most of the text of 312.23 is devoted to emphasizing that the amount of information is flexible and appropriate for the stage of investigation. Simply put, there are no significant GMP requirements in 211. This justification for issuing the direct final rule is false.

5. FDA repeatedly points to the guidance document to replace the requirements of 211. FDA does not enforce guidance documents; a government agency relying on guidance invites misunderstandings and inconsistencies.

The guidance document fails to address important questions. The guidance document will not go through the same level of notice and comment, and therefore it lacks the complete input of interested parties. If this were not the case, FDA would issue the guidance as a regulation.

6. FDA does not have the expertise to issue guidance or regulation without stakeholder input. The manufacture of clinical supplies is a complex matter in which the FDA has almost no experience. While FDA routinely inspects commercial production, FDA lacks expertise in clinical GMP compliance because FDA has performed few inspections of early clinical supply material. FDA typically inspects a product for the first time at the Pre-Approval

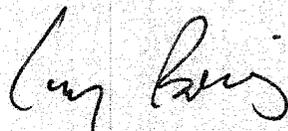
Inspection performed at the end of the pivotal Phase 3 trial. With rare exceptions, PAIs inspect facilities and operations that are far different from those used for Phase 1.

Since the FDA is interested in speeding product development, the FDA should welcome the opportunity to work with the industry to address industry-wide questions about quality for clinical trial materials. In crafting a regulation, a substantive discussion about the appropriate level of compliance would include the following points.

- Equipment Qualification. What is the appropriate qualification for complex equipment such as a lyophilizer?
- Water Quality. When is WFI required? Are the requirements different from commercial products, and why?
- Method Validation or Qualification. If "full validation" is not required, then what is required? A protocol with acceptance criteria? Independent review of the report? Precision? Accuracy?
- Sterility Assurance. What media fills are needed for very small lots?
- Control of Contractors.
- Complaints. What are the requirements to address product quality complaints from a CRO?
- Cleaning. What criteria and methods are appropriate when the dosing information is incomplete?
- Specifications. Can specifications be changed to make a batch pass *post hoc*?

By exempting Phase 1 materials from 211 without a replacement, FDA leaves the industry with only a guidance document into which the industry and other interested parties have had no input. In the rare but foreseeable event that a Phase 1 company is inspected, what standard will the investigator apply?

I urge the FDA to withdraw the direct final rule and engage the industry in a meaningful and formal discussion to balance product development with patient safety.



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