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Joan Claybrook, President

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Current Good Manufacturing Practice Regulation and Investigational New Drugs (Docket No. 2005N-0285)

To whom it may concern:

Well, at least the proposal, from the perspective of the benefits to industry, is honest. As the Preamble clearly states, “This action is intended to streamline and promote the drug development process while ensuring the safety and quality of [drugs for use in] Phase 1 clinical trials.” The advantages to industry of the proposal, in terms of reduced production requirements, cost, oversight and accountability are clear. And while the public health problem purportedly addressed by the proposal is fewer new drugs entering clinical trials due to excessive red tape, the proposal fails to even make the slightest case that this is so or that overregulation is somehow responsible. We therefore call on the agency to withdraw the Direct Final Rule and permit full notice and comment on its proposal.

Under the current regulatory regimen, all drugs, whether investigational or not, are subject to the Good Manufacturing Practice (GMP) guidelines laid out in 21 CFR 211. The GMP requirements address, in a comprehensive fashion, the soup-to-nuts of quality drug production: personnel, plumbing, waste disposal, lighting, batch production, laboratory records, etc. The regulations have stood us in good stead. Any attempt to reduce the applicability of 21 CFR 211 not only invites greatly reduced production standards, but also leaves the FDA relatively powerless to take remedial action. Yet, that is precisely what is proposed: the exemption of many drug and biological products for Phase I trials from the rigors of 21 CFR 211.

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). From the perspective of any patient injured by a GMP-violating drug in a Phase I study, it will be cold comfort that the FDA deemed following accepted standards too cumbersome. If some company or academic laboratory cannot follow GMPs, they should probably not be in the practice of preparing drugs for administration to humans.

Instead of the detailed, enforceable standards laid out in 21 CFR 211, the FDA proposes to rely upon three sources of authority that are variously lacking in detail and/or unenforceable. The first source is FDA’s general statutory authority, 21 USC 351 (a)(2)(B), which is literally only a sentence long and essentially states that the product must be manufactured according to GMP. (Of course, the present proposal then removes the specifics of GMP compliance for many Phase I products by exempting them from 21 CFR 211.) Second, the agency claims it can maintain adequate production standards under the Investigational New Drug submission requirements at 21 CFR 312.23. But these, too, contain nowhere near the detail in the “offending” 21 CFR 211. Instead, we get only

generalities under 21 CFR 312.23, which is really intended to describe the contents of an Investigational New Drug submission package. Of course, there is a requirement for describing “chemistry, manufacturing, and control information,” but to really understand how to do this, one would need to refer to 21 CFR 211 (which now would no longer apply to many Phase I products). Third, instead of the clear, enforceable standards of 21 CFR 211, the FDA puts forth a voluntary guidance that is still in draft form and may never be finalized. Like all FDA guidances, it comes replete with assurances of how unenforceable it is: “This draft guidance ... does not create or confer any rights for or on any person and does not operate to bind FDA or the public ... FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities.”

As if to ironically illustrate just how toothless FDA guidances are, the agency has actually violated one in promulgating the Direct Final Rule. FDA’s November 21, 1997, guidance on Direct Final Rule Procedures explains the conditions under which the agency will put forth such rules, which by design curtail notice and comment procedures:

FDA will only use direct final rulemaking procedures when the agency expects that there will be no significant adverse comment. For example, FDA will consider direct final rulemaking for minor, substantive changes to regulations; incorporation by reference of the latest edition of technical or industry standards; extensions of compliance dates, direct incorporations of mandates from new legislation; and other non controversial rules where FDA determines that use of direct final rulemaking is in the public interest and that the rule is unlikely to result in any significant adverse comment.

Clearly, none of these conditions are not met in the current case. The agency has published both the Direct Final Rule and a nearly identical Proposed Rule, which it will withdraw if no significant adverse comments are received. Nonetheless, the agency’s antipathy toward public notice and comment is evident.

The recent disaster with TGN1412, in which six healthy Phase I volunteers had to be placed on ventilators, some comatose, may not seem relevant to this FDA proposal. But in Britain, which has not sought to absolve drugs for Phase I trials of the requirement 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.

The reason we have GMPs is because manufacturing drugs is a difficult task best not left to amateurs. Only people with the requisite expertise, backed up by appropriate regulatory authority, should undertake the task. Healthy volunteers and patients with advanced diseases place their bodies on the line in Phase I studies, hoping to improve medical outcomes for later generations. The least they deserve is a properly manufactured drug.

Sincerely,

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