

September 1, 2004

David A. Lepay  
Office for Science and Health Coordination  
Good Clinical Practice Programs (HF-34)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: Docket No. 204N-0018: Human Subject Protection; Foreign Clinical Studies not Conducted Under an Investigational New Drug Application

Dear Dr. Lepay:

Beneath the seemingly innocuous veneer of this proposal to require foreign clinical studies conducted without a U.S. Investigational New Drug application (IND) to comply only with Good Clinical Practice (GCP) guidelines is FDA's ongoing pursuit of a long-held goal: the undermining of the Declaration of Helsinki (DOH) as the international touchstone for the ethical conduct of clinical studies. This agenda began with a series of articles by Food and Drug Administration (FDA) employees that raised questions about certain DOH principles.<sup>1,2,3,4,5,6</sup> It continued with FDA efforts to weaken both the DOH and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects, and has now reached its apotheosis in this proposal that would literally purge any reference to the DOH from FDA drug regulations.

The last decade has seen an exponential growth in the number of foreign clinical trials, including those conducted in developing countries. The number of new foreign investigators in the FDA's database grew from 988 in the 1990-1992 period to 5,380 in the 1996-1998 period.<sup>7</sup> Some of these studies were preceded by INDs, which allow a company to administer a drug under investigation to humans, while others were not. For example, a Swedish drug manufacturer might decide to conduct a study of a new drug in Sweden and/or other non-U.S. countries and the study may never come to the attention of the FDA until the company seeks approval in the United States. In that case, current FDA regulations require the studies submitted to have been conducted in a manner consistent either with the DOH or any local laws, whichever is more protective for patients.<sup>8</sup> The FDA's current proposal would remove this requirement and require instead that the submitted studies only be consistent with the GCP guidelines of the International Conference on Harmonisation (ICH).

The DOH is not a perfect document. But at least it has the virtue of being the product of a quasi-democratic process. The DOH is produced by the World Medical Association, which in turn is comprised of 82 national medical associations such as the American Medical Association. The DOH can only be amended with a formal vote before the full World Medical Assembly, which meets annually. By contrast, the ICH guidelines, of which the GCP<sup>9</sup> is but one, are the product of negotiations by just six parties: the regulatory authorities and pharmaceutical industries of the U.S., the European Union and Japan. Consumer and developing country input into the development of the ICH guidelines asymptotically approaches zero. (The GCP guideline has been formally adopted as a Guidance by the FDA and parts of it have been incorporated into FDA regulations.<sup>10</sup>)

The FDA offers three reasons for revising its regulations on foreign non-IND research:

1. International ethical standards have been updated recently. This is certainly true, but what is left unsaid is that the FDA has objected to many of the substantive changes in the updates, particularly the DOH. These are the true source of the FDA hostility toward the DOH. (We shall not reargue the merits of these particular changes, as our positions have been repeatedly made clear and are available in numerous publications on our website.<sup>11</sup>)

In particular, the FDA has been a leading force in attempts to undermine restrictions on placebo use in clinical trials, both domestically and abroad (DOH, Paragraph 29). For example, in a forthcoming book chapter, an FDA employee will defend the use of placebos in developing countries even when the condition under study is life-threatening and the country has approved effective drugs for the condition. Ironically, Paragraph 29 has already been weakened due, in significant part, to FDA objections (as a result, a confusing “clarification” was added to the DOH), but the agency is apparently not yet satisfied.

The Department of Health and Human Services (which includes the FDA) has also objected to the extremely reasonable DOH requirement that effective medications be provided to all study participants at the conclusion of the research (Paragraph 30).<sup>12</sup> FDA’s efforts to undermine this Paragraph may also yield fruit, as the WMA Council has adopted yet another “clarification” that seeks to weaken the stronger language in the actual body of the DOH. Although the FDA may not be on record with respect to Paragraph 19, which requires that the local community benefit from the research, this may be an additional source of FDA discontent.

2. “Ensuring quality of data.” We, of course, share this goal and there is no question that the GCP Guidance goes some way to securing this end. But it is a document designed to improve data quality and is not primarily concerned with research ethics. Of course, some aspects of ethics do come up (e.g., ethics committees, informed consent), but on the whole the GCP Guidance is concerned with procedural issues, not overarching ethical ones. The Guidance does not, for example, address conflict of interest or the need to publish results, topics included in the DOH. The Guidance and the DOH are thus

complementary documents and there is no reason that the regulations could not require that the affected studies comply with both.

3. The DOH could be modified “independent of FDA authority.” However, the agency does acknowledge that any revisions “could not supersede U.S. laws and regulations.” It is also true that the ICH might modify the GCP guidelines, perhaps triggering a change in the FDA regulations. The FDA has already demonstrated its ability to evade the 2000 improvements in the DOH by declaring in 2001 that the reference to the DOH in FDA regulations was actually to the 1989 version.<sup>13</sup> Exactly what, then, is the problem?

We also note that the reference to compliance with the laws of the host country has been removed from the proposed regulation. While it is certainly not the FDA’s job to police other countries, the notion that the FDA could accept data collected in violation of local host country laws does not send an appropriate message to pharmaceutical companies who see the United States as their main market and might be willing to breach the law in less-important markets as part of an effort to secure FDA approval.

In closing, the effort to strike reference to the DOH is sadly reminiscent of unilateral U.S. actions in other spheres. From the International Criminal Court to the Kyoto Treaty, the Treaty on the Limitation of Anti-Ballistic Missile Systems, the Biological Weapons Convention, the Comprehensive Test Ban Treaty, and the (Land) Mine Ban Treaty, the United States has developed a flair for exceptionalism to international standards. The DOH is the standard-bearer for international research ethics and enjoys particular respect in the developing world. It would be tragic if this assault on the DOH fell in line with other U.S. efforts to flout international mores.

Yours sincerely,

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<sup>1</sup> Temple RJ. Special study designs: early escape, enrichment, studies in non-responders. *Communications in Statistics* 1994;23:499-531.

<sup>2</sup> Temple RJ. When are clinical trials of a given agent vs. placebo no longer appropriate or feasible? *Controlled Clinical Trials* 1997;18:613-20.

<sup>3</sup> Temple RJ. Problems in interpreting active control equivalence trials. *Accountability in Research* 1996;4:267-75.

<sup>4</sup> Temple R. Difficulties in evaluating positive control trials. *Proceedings of the American Statistical Association, Biopharmaceutical Section*. 1983:1-7.

<sup>5</sup> Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Annals of Internal Medicine* 2000;133:455-63.

<sup>6</sup> Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. *Annals of Internal Medicine* 2000;133:464-70.

7. Office of the Inspector General. Recruiting human subjects: pressures in industry-sponsored clinical research. Department of Health and Human Services, June 2000.

<sup>8</sup> 21 CFR 312.120(c)(1)

<sup>9</sup> International Conference on Harmonisation. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance. April 1996. Available at: [www.fda.gov/cder/guidance/959fnl.pdf](http://www.fda.gov/cder/guidance/959fnl.pdf).

<sup>10</sup> 62 Fed Reg 25692, May 9, 1997.

<sup>11</sup> <http://www.citizen.org/hrg/>

<sup>12</sup> Koski G, Nightingale SL. Research Involving Human Subjects in Developing Countries. *New England Journal of Medicine* 2001;345:136-8.

<sup>13</sup> Food and Drug Administration. Guidance for Industry: Acceptance of Foreign Clinical Studies. March 2001. Available at: <http://www.fda.gov/ohrms/dockets/98fr/010079g2.pdf>.