

# United States Senate

WASHINGTON, DC 20510

July 15, 2004

The Honorable Lester M. Crawford, D.V.M., Ph.D.  
Deputy Commissioner for Food and Drugs  
U.S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857-0001

Dear Commissioner Crawford:

Over the past several weeks, news reports have brought to light the need for the Food and Drug Administration (FDA) to: (1) ensure that drug companies are fully reporting adverse events associated with their products, whether investigational or approved drugs; (2) work with NIH and the regulated industry to expand public information about ongoing clinical studies; and (3) make publicly available, or work with product sponsors to ensure public availability of, the results of clinical studies, whether positive or negative. We would appreciate your agency's response to questions we have regarding each of these issues.

First, drug companies are required to report to FDA data regarding adverse events, whether those products are in clinical trials or already approved for sale. The FDA has also been given additional funding in recent years by the Congress, as the FDA has noted, to "protect human subjects and the integrity of research data in clinical trials." This includes the protection of patients enrolled in clinical trials and assuring that companies are appropriately reporting adverse events to the FDA. Unfortunately, certain drug companies have failed in important instances to disclose significant data regarding adverse events for the patients enrolled in clinical trials.

There is also a more basic question of whether drug manufacturers are fully reporting the existence of clinical studies of drugs and biological drug products to treat serious or life-threatening diseases in accordance with provisions of the Food and Drug Administration Modernization Act (FDAMA, P.L. 105-115). The law encourages that all such clinical studies, whether publicly or privately funded, be listed on a publicly accessible database maintained by the National Library of Medicine (NLM).

However, a large number of trials are not reported to NLM and thus are never known to patients who might benefit from them. As an article entitled "Drugmakers Prefer Silence On Test Data" in the *Washington Post* on July 6, 2004, states, "An FDA analysis found that in 2002 only 48 percent of trials of cancer drugs had been registered, and a preliminary review now indicates the listing rate for drugs for some other serious diseases is in the single digits. Some companies have listed no studies; some trials are listed without identifying the sponsoring company or the drug being tested."

As a result, the American Medical Association (AMA) has recently called for the creation of a more thorough centralized clinical trials registry “so that scientists, investigators and clinicians could easily find information on trials.” We would add that consumers should also have access to such a list.

Finally, and of great importance, is the failure of drug companies to disclose important data to the FDA and the public about the outcomes of clinical studies, particularly those that produce negative results. It is especially distressing that such results are not made known for many clinical drug trials involving children and adolescents as was encouraged by the “Best Pharmaceuticals for Children Act” (P.L.107-109) and the “Pediatric Research Equity Act” (P.L. 108-155). The value of such studies, and the expectations of the legislation, are limited at best if study results – both positive and negative – are not made fully available.

Ethical concerns about the failure to report all results have also been raised by experts. As Drs. Julie Magno Zito, Albert T. Derivan, and Laurence L. Greenhill noted in an article published in the May 1, 2004, edition of the *Journal of the American Academy of Child and Adolescent Psychiatry*:

*The responsibility to make available the results of clinical studies stems directly from the ethical principle of justice. Nearly 25 years ago, the Belmont Report delineated three ethical principles, the application of which was intended to provide protection for human subjects of research. These principles, namely, respect for persons, beneficence, and justice, are now cornerstones of modern bioethics. The principle of justice was initially applied to the selection of research subjects. It specifies that those who bear the risks associated with clinical studies should also reap the benefits, whether this occurs directly through the experimental treatment or indirectly through the societal benefit of advancing knowledge about the condition being studied...Assuring subjects that research findings from all studies, whether proprietary or in the public domain, will be made available is a clear application of the justice principle.*

Furthermore, as the AMA Council on Scientific Affairs indicated, “This pattern...distorts the medical literature, thereby affecting the validity and findings of systematic reviews and meta-analyses, the decisions of funding agencies, and ultimately the optimal practice of medicine.”

To address this, Drs. Zito, Derivan, and Greenhill have recommended that “(1) there must be full recognition of the ethical imperative to publish all data from clinical trials in a timely manner – this must include negative as well as positive studies, without exceptions; (2) the FDA and other regulatory bodies must act in a fully transparent manner – recommendations from these agencies must be based upon data that are readily available for public education and review; and (3) a registry of all pediatric psychopharmacology trials should be placed in the public domain when such trials are begun – this will help to ensure that the results of these trials will eventually be made public.”

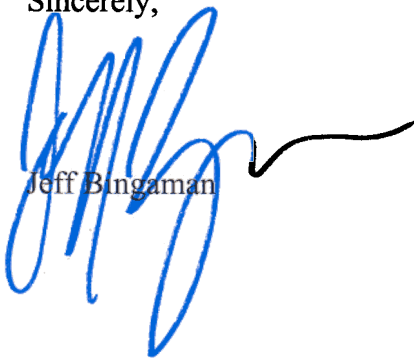
These issues raise a number of important questions that we wish to bring to your immediate attention:

What actions does FDA plan to take to ensure that drug trial sponsors respond to the current federal clinical trial reporting provisions under FDAMA?

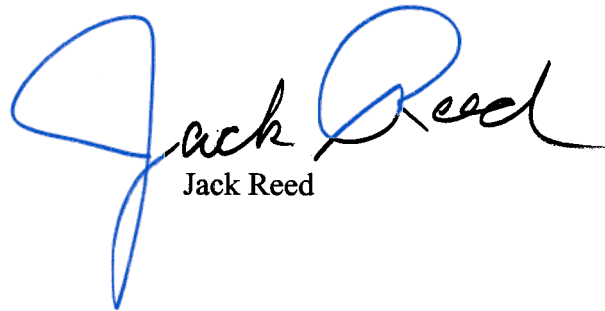
- What is the status of the public database of adverse events FDA is considering?
- What will be done to ensure maximum public accessibility to this adverse event information and as well as compliance by manufacturers?
- Is FDA willing to pursue making clinical trials registration a condition of approval of a protocol, or consider making institutional review board approval contingent upon registration, as the AMA has recommended? Would FDA's ability to hold up clinical studies pending the sponsor's commitment to list the trial require any change in law to provide specific authority for the agency to do this?
- How does your agency respond to the recommendations set forth by Drs. Zito, Derivan and Greenhill and is there anything FDA is planning to do to address these concerns?

We would greatly appreciate your prompt response to these questions. Thank you for your consideration of these critical issues, and we look forward to hearing from you.

Sincerely,



Jeff Bingaman



Jack Reed