United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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Grassley says FDA has duty to protect people who participate in clinical drug trials

WASHINGTON — Sen. Chuck Grassley is calling on the Food and Drug Administration to implement recommendations stemming from an independent review of the agency's oversight of clinical trials involving human subjects.

"We're all in debt to the individuals who volunteer for the clinical trials that advance medicine and lead to lifesaving cures. The Food and Drug Administration needs to make sure these human subjects are treated properly and fully informed," Grassley said.

Grassley made his appeal in a letter to the FDA Commissioner. The text is below. The report of the Inspector General for the Department of Health and Human Services containing the recommendations is posted at http://finance.senate.gov, along with this news release.

September 27, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under those programs to oversee the proper administration of the programs, including the payment for prescription drugs regulated by the Food and Drug Administration (FDA or Agency). As Ranking Member of the Committee, I have the duty to ensure that FDA upholds its responsibility to the public's safety by properly regulating the nation's drug supply and ensuring that the drugs Americans use are safe and effective.

Almost two years ago, I initiated a review of the clinical trial system to assess the limitations of current oversight in ensuring protections for human subjects of clinical research. More specifically, during the course of a number of investigations that I conducted, serious concerns came to light regarding, among other things, inadequate human subject protections, including insufficient warning of risks associated with a clinical trial. Accordingly, and in part because of these concerns, I asked the Department of Health and Human Services Office of Inspector General (HHS OIG) to examine FDA's oversight of clinical trials. HHS OIG recently completed its review of FDA's processes for inspecting clinical trials. In particular, the OIG looked at the bioresearch monitoring inspections of sponsors, clinical investigators, and institutional review boards (IRBs) that are conducted by FDA's Office of Regulatory Affairs (ORA).

HHS OIG found a number of troubling facts regarding the FDA's oversight of clinical trials. For example, FDA does not keep an internal clinical trial registry, is unable to identify all ongoing clinical trials, and does not keep a registry of Institutional Review Boards (IRBs).

The OIG also determined that the Agency "does not consistently track inspection information," and inconsistently classifies inspections. For example, HHS OIG found that the Center for Drug Evaluation and Research (CDER) disagreed with almost 70 percent of ORA's recommendations for Official Action Indicated (OAI) and changed the classifications to Voluntary Action Indicated (VAI). OAI would mean that ORA found and documented "objectionable" conditions or practices during its inspection that warrant further regulatory or administrative action by the Agency, such as a warning letter, whereas VAI means the conditions or practices were not serious enough for the Agency to take action. In other words, CDER often downgrades the seriousness of the clinical trial violation. To add insult to injury, CDER would make these downgrade changes without systematically tracking its reasons for the change.

The HHS OIG also noted that the FDA must conduct follow-up inspections of individuals to ensure that previously inspected individuals do not repeat violations in future clinical trials. Yet HHS OIG found that the centers do not track responses to warning letters or other letters issued to an inspected entity pursuant to an OAI determination. What further troubles me is that HHS OIG found that FDA rarely conducts follow-up inspections.

In addition, the HHS OIG raised concern that most inspections occur after the conclusion of a trial. In light of this, FDA "cannot ensure that sponsors, clinical investigators, and IRBs are taking the necessary actions to protect human subjects during the trials." (emphasis added) Interestingly, FDA staff members raised this same concern during their interviews with my Committee staff regarding the large safety study of the antibiotic Ketek that was conducted in 2002. The HHS OIG also confirmed problems that I highlighted almost two years ago that FDA is doing fewer and fewer inspections of IRBs, which in my mind translates into trouble for those individuals who volunteer to participate in clinical trials.

Accordingly, I request that FDA arrange a briefing for my Committee staff to address these concerns and the HHS OIG findings by no later than November 5, 2007. In particular, please have your staff prepared to answer the following questions, among others, during the briefing:

1. Given HHS OIG's findings regarding the lack of tracking of inspections and follow-up, what does the FDA do to ensure that corrective actions are taken and sustained?

2. According to HHS OIG, its review of FDA inspection files show that the most common reason for changing an OAI to a VAI was a center's and FDA's Office of Chief Counsel's determination that the violations were not serious enough to send a warning letter and that the inspected entity "promised corrective actions." Please describe the types of violations that ORA classified as OAI, but were subsequently changed to VAI by a center during the period of January 2002 through December 2006.

3. As HHS OIG pointed out, the frequent reclassification of ORA recommendations from OAI to VAI by the centers suggest that "ORA and the centers sometimes interpret the regulations and guidance for BiMo inspection classifications differently." What actions, if any, is the Agency taking to address the high percentage of reclassifications of ORA recommendations?

4. In June 2006, FDA announced that the Agency was working on a proposed rule for companies to report clinical trial fraud. What is the status of that proposal? Please identify the number of clinical trial fraud reported voluntarily by companies, by year, over the last five years.

5. According to an FDA official interviewed by HHS OIG, about 20 to 25 percent of the trials for products that FDA oversees occur outside of the United States, and this number is growing. Because FDA's regulations generally do not apply to trials conducted outside of the United States, the Agency's oversight of foreign trials is limited. What steps, if any, is the FDA taking to ensure the quality and integrity of data from foreign clinical trials, and what is the Agency doing to improve its monitoring of such trials?

6. What tools does the FDA need to improve its access to and oversight of clinical trials conducted outside the United States?

I look forward to your cooperation and assistance on this important matter. The HHS OIG recommended steps that FDA can take to improve its oversight of clinical trials. Please keep me apprised of the status of FDA's implementation of HHS OIG's recommendations as well as the Agency's initiatives for improving clinical trials monitoring on a quarterly basis beginning on November 5, 2007.

Sincerely,
Charles E. Grassley
Ranking Member