Department of Health and Human Services

# OFFICE OF INSPECTOR GENERAL

# The Globalization of Clinical Trials

## A Growing Challenge in Protecting Human Subjects

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# EXECUTIVE SUMMARY

## PURPOSE

To document the growth of non-U.S. clinical drug trials contributing data to New Drug Applications for Food and Drug Administration (FDA) approval, and to assess FDA's capacity to assure human subject protections in these trials.

## BACKGROUND

In our June 2000 report, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* (OEI-01-97-00195), we drew attention to the fact that clinical drug trials conducted outside the U.S. can be an important source of data in FDA's determination of the safety and efficacy of new drugs. Pharmaceutical companies submit trial data to FDA as part of a New Drug Application, the application for FDA approval to market a drug in the U.S. Although the majority of foreign clinical drug research that is submitted in New Drug Applications is still conducted in countries with a history of clinical drug research, increasingly, countries with less experience are emerging as desirable locations for sponsors to conduct this research.

In conducting this inquiry, we analyzed two FDA databases: one of clinical investigators conducting drug research and one of clinical investigators conducting drug research who have been inspected by FDA. We interviewed FDA officials and industry representatives. We also reviewed pertinent FDA documents and related literature.

## FINDINGS

### FDA oversees significantly more foreign research than it did 10 years ago.

The number of foreign clinical investigators conducting drug research under Investigational New Drug Applications increased 16-fold in the past decade. In 1990, 271 of these foreign clinical investigators were in FDA's database. By 1999 the number grew to 4,458. FDA inspections of foreign clinical investigators conducting drug research have also increased dramatically, from just 22 in 1990 to 64 in 1999.

### Sponsors have expanded research sites into many countries that appear to have limited experience in clinical trials.

The number of countries in which clinical investigators conduct drug research that is tracked by FDA increased from 28 in 1990 to 79 in 1999. Among the countries that have experienced the largest growth in clinical investigators are Russia and countries in Eastern Europe and Latin America. Sponsors explain this growth by pointing to readily

accessible human subjects, potential new markets for approved drugs, and recent international agreements that ease FDA acceptance of foreign research data. Contract research organizations are also moving into these areas. FDA is also beginning to inspect investigators in areas where FDA-regulated research has not previously been conducted.

### FDA cannot assure the same level of human subject protections in foreign trials as domestic ones.

FDA receives minimal information on the performance of foreign institutional review boards. It does not inspect these boards, nor does it tend to receive much information from the host countries of these boards. It cannot necessarily depend on foreign investigators signing attestations that they will uphold human subject protections. It has an inadequate database on the people and entities involved in foreign research.

### Key entities overseeing or studying foreign research have raised concerns about some foreign institutional review boards.

The pharmaceutical industry, national regulatory agencies, the National Bioethics Advisory Commission, and the World Health Organization have all raised concerns about some of the institutional review boards that review research at foreign sites. Their concerns tend to focus on the boards' lack of experience and insufficient monitoring practices.

## RECOMMENDATIONS

The purpose of these recommendations is to help ensure that the protections provided for foreign clinical drug research are at least equivalent to U.S. regulations, not to discourage the submission of non-U.S. data. We direct most of our recommendations to FDA, since it has the jurisdiction for the commercially funded research that was the focus of our inquiry. We also make recommendations to the Office for Human Research Protections, which is in a prime position to foster integrated approaches to protecting human subjects across Federal agencies.

We recognize that FDA has taken many important steps in strengthening human subject protections despite the difficulties of limited resources and limited information about foreign research. In recommending an increase in human subject protection efforts, we also acknowledge that all efforts in this area must be respectful of the sovereignty of other countries and compatible with harmonization efforts. Furthermore, we recognize that some of our recommendations may require additional resources.

### We recommend that FDA:

**Obtain more information about the performance of foreign institutional review boards**. By working with the regulatory authorities in foreign countries to

obtain information about the practices of local institutional review boards, or more directly by assisting in inspections, FDA can address its lack of information about the adequacy of foreign institutional review boards' review of human subject protection issues in clinical research submitted in New Drug Applications.

**Help foreign boards build capacity.** By working with the Office for Human Research Protections, the National Institutes of Health, and others, FDA can help newly established foreign review boards conduct effective human subject reviews.

**Encourage sponsors to obtain attestations from foreign investigators.** By encouraging attestations from non-U.S. investigators stating that they will adhere to ethically sound principles of research, FDA can promote adherence to ethical guidelines. Foreign investigators working under an Investigational New Drug Application should sign attestations, as Investigational New Drug Application regulations require. Similarly, foreign investigators working under other research guidelines could be encouraged to sign a statement of their intention to comply with the guidelines they follow.

**Encourage greater sponsor monitoring.** By encouraging more rigorous monitoring of foreign research sites by sponsors and their agents, FDA can reinforce their responsibility to ensure human subject protections. FDA can work with sponsors to achieve a clearer mutual understanding of the roles they can play in that regard.

**Develop a database to track the growth and location of foreign research.** Given the significant growth occurring in non-U.S. research submitted as part of New Drug Applications, it is important for purposes of oversight and resource allocation that FDA have more and better information about key elements of that growth.

**Finally, we recommend that the Office for Human Research Protections:**

**Exert leadership.** By developing strategies to ensure that adequate human subject protections are afforded for non-U.S. clinical trials that are funded by the Federal government and/or that contribute data in support of a New Drug Application, the Office for Human Research Protections can exert leadership. It is already moving in this direction. In its leadership role, it can foster integrated approaches that would apply across Federal agencies and to federally funded and New Drug Application research conducted at non-U.S. sites.

**Encourage accreditation.** Encouraging participation of institutional review boards in a voluntary accreditation system is one way to improve the capacity to conduct appropriate reviews of human subject protections in proposed research. The Office for Human Research Protections, working with FDA, NIH, and others, can help develop such a system internationally.

## COMMENTS ON THE DRAFT REPORT

Within the Department of Health and Human Services, we received comments from the FDA and the Office for Human Research Protections (OHRP). The OHRP concurred with the two recommendations we directed to it and stressed its readiness to engage in the kind of leadership we called for. The FDA supported all of our recommendations except for the one calling for better data collection on foreign research. It indicated that the purpose and methods we presented concerning the recommendation were not sufficiently clear. In this final report, we modified the recommendation to more clearly define the goal for FDA to develop a database to track the location and growth of foreign research. Such a data base, we suggest, can be helpful in guiding FDA oversight and setting priorities. We also suggested one way to begin gathering such data as well as a broader strategy for the future.

FDA emphasized its lack of resources and its limited authority in foreign countries as constraints in carrying out the remaining recommendations. While we agree that these are limiting factors, we believe the FDA can use its technical expertise, its influence as the approving authority for drugs marketed in the U.S., and its prestige and experience in international circles to promote reforms even in foreign countries.

External to the Department, we solicited comments from the Pharmaceutical Research and Manufacturers of America (PhRMA), Public Citizen Health Research Group, Public Responsibility in Medicine and Research (PRIM&R), and Applied Research Ethics National Association (ARENA). The following is a summary of the comments we received: PRIM&R and ARENA urged FDA "require" not as we suggested "encourage" investigator attestations for foreign research used in support of New Dug Applications. But in general the two organizations supported our recommendations. Public Citizen was more critical, indicating that our recommendations were not strong enough in light of the problems we identified. The comments of these organizations warrant consideration and reinforce our central concern: that FDA cannot assure the same level of protections in foreign trials as domestic ones.