# The "Weak Link" in New Drug Research

No matter how critically we might examine the subject, there is no denying that the United States has a very comprehensive set of laws and regulations governing the research, testing, development, manufacture, packaging, promotion, and marketing of new drugs intended for human use. All of this did not come about overnight, nor without various triggering incidents—usually adverse—along the way that prompted Congress to enact new legislation or the Food and Drug Administration to adopt pertinent additional regulations.

The present result is that virtually each of the steps listed above now entails very elaborate, complex facilities, personnel, and equipment. No longer is the drug manufacturing business a viable activity for "the little guy." By yesterday's standards, even the smallest drug companies today are rather large, and they are only "small" in comparison to the giants and near giants that are their "friendly competitors."

For the most part, this development has been a good one because it has resulted in more highly qualified personnel, better equipment, and an overall improved standard of manufacturing performance. Long gone is the "cottage industry" dimension of the U.S. pharmaceutical industry.

At least, long gone in every area except one. And, unfortunately, that remaining area is proving to be the most serious weak link in the entire continuum that eventually leads to the successful marketing of an important new drug.

We are referring to clinical testing, and the fact is that even the largest drug companies conduct very little clinical research themselves. Traditionally, such testing is done by independent clinical investigators affiliated with universities, or teaching hospitals, or operating as very small testing laboratories.

Many disinterested observers have considered this to be a good arrangement; in fact, many of us have regarded it as the preferred one. We have thought that such independence would result in more truthful, reliable, and objective testing and test reporting.

Naturally, as with every aspect of life, we expected that there would be some flaws in this system; that some investigators would be charlatans; and that some drug firms might succeed in getting certain drugs approved that otherwise would not quite make it. Indeed, because of some abuses years ago, the FDA had found it necessary to adopt procedures designed to assure that only qualified investigators are engaged in clinical drug testing; that their facilities, record-keeping practices, and general operating procedures adhere to acceptable standards; and that there is a system for disqualifying, censuring, and permanently barring violators.

But drug testing is far from being an exact science, and despite these safeguards, certain investigators began to develop informal reputations as being far more likely to produce a test report favorable to the drug under study than if it were tested by most other investigators in the field. In turn, this induced at least some drug firms to engage in "investigator shopping." Such "shopping" would not be with the idea of being charged a lower fee for the work, but rather with the objective of benefiting from the conscious or unconscious bias of certain investigators.

But apparently, these personal propensities were equally apparent to the FDA as they were to the drug firms, and most companies quickly concluded that their drugs would fare far better in the FDA review process if they had been tested by one or more of the clinical investigators who enjoy a reputation for being tough critics in their work.

So it appeared that the system—though ever so delicately balanced—would survive and would continue to fulfill its purpose in an acceptable manner.

Sadly, however, the system was recently dealt a severe blow which causes us to reconsider our long-held belief that the independent clinical investigator system must be maintained and preserved at all costs. Specifically, there has been a rash of cases of fabricated or falsified data, and they have come from some very highly respected clinical investigators.

Indeed, the severity of the problem recently prompted *The Washington Post* to run a lead article headlined "FDA, Citing Phony Evidence, Bars Drug Tests by Researcher," and subtitled "Wave of False Medical Experiments." This March 23 article specifically reports on the chicanery of a "leading heart specialist," who is named and quoted in the article.

"The case is one of the most important in a wave of phony medical testing that is raising new concerns in federal health agencies, which rely heavily on such data to help them determine a drug's safety and effectiveness," according to the article in the *Post*.

An NIH staff official is quoted as saying that until about 1980 cases of phony medical research by NIH grantees came up rarely, "perhaps once every other year," but since then such cases "are cropping up so often, they can't be dealt with as isolated events."

The article went on to cite other facts and figures including: (*a*) seven physicians have signed a new type of "consent agreement" with FDA that they will not test future investigational drugs, (*b*) FDA's ruling of eight other physicians as ineligible to receive investigational drugs, and (*c*) several criminal prosecutions of investigators during the past year.

But the article focused on the heart specialist because it pointed out that "(his) prominence, however, makes his case stand out." He was an FDA outside advisor for six years; he was the president of a prominent society of cardiologists; he published over 200 scientific papers; he served as an advisor for 21 professional journals; and he has been a formal "consultant to numerous federal and state agencies, the American Medical Association's Department of Drugs, and the American Heart Association."

Undoubtedly, there are still many honest and reliable clinical investigators. However, these recent experiences show that the present system is no longer reliable, and therefore it is no longer acceptable. If we are misled as to whether the drug entity itself is effective, what purpose is served by elaborate good manufacturing practice requirements, extensive quality control protocols, or scrupulous adherence to rigid advertising limitations? Indeed, the clinical testing is the very heart of the entire process.

Whenever past defects at one point or another in that process have been uncovered, Congress, the FDA, or the scientific community—individually or collectively—have moved to institute corrective changes. It appears that such changes must now be made in this last of the drug-related "cottage industries," if we are to have continued confidence in the effectiveness of our new drug supply.

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