Improving the Reliability of Clinical Investigators

[Editor's note: The May 1983 editorial triggered an exchange of letters between former FDA Commissioner Jere E. Goyan and the author of the editorial, Edward G. Feldmann. In the interest of stimulating further thought on the important subject dealt with in the editorial, they have agreed to publication of their correspondence which follows herewith.]

Goyan letter to Feldmann, dated June 2, 1983:

Just a note to let you know that I read your editorial[1] entitled "The 'Weak Link' in Drug Research." I was somewhat astonished at your analysis and conclusions but understand your concerns. Indeed, one of the biggest shocks of my life was the opportunity to review some of the proposed disciplinary actions against clinical investigators. It is distressing to learn that many of the people in the "white hats" are at least somewhat gray, if not black. However, I am a little hard pressed to understand what alternatives we might have in this regard. It seems to me that we are going to have to make use of clinical investigators in academic settings, but unfortunately we may have to devote more resources to their policing. In any case, it was as usual a very provocative and worthwhile editorial.

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Received June 6, 1983.

[1] E. G. Feldmann, *J. Pharm., Sci.*, **72**, 463 (1983).

Feldmann letter to Goyan, dated June 7, 1983:

Last week I attended an FDA retirement dinner and reception and had an opportunity to chat with various FDA staff members from new drug officers to enforcement/compliance people to legal staff, and I was frankly surprised at how many of them apparently had read the editorial, brought it up in conversation with me, and expressed their personal concerns regarding the reliability of clinical investigators and their data submitted in support of NDAs. It was quite apparent to me that I had hit a responsive chord among the FDA staff.

I fully understand your comments as to the difficulty in identifying alternatives to our present system. I am not sure that I have any magical answers either, and for that reason did not attempt to include any in the editorial.

However, it would seem to me that arrangements could be worked out which would involve individuals (clinical investigators) who are *employees* of drug firms being based physically at hospitals or in academic settings which would enable them to conduct investigations in much the same environment and with the same basic *modus operandi* that is presently utilized—the only significant difference being that rather than functioning as independent contractors, they would actually be employed by the drug company involved.

In a sense, it might be argued that this kind of arrangement would result in somewhat less "independence" or "independent authority" on the part of the clinical investigator. Although that argument (for "independence") sounds good in theory, in practice there appear to be certain drawbacks:

(a) The company, *per se*, is not responsible for the actions of the clinical investigator, and it can readily disclaim responsibility if there is any "hanky panky."

(b) A conscientious drug firm has its hands tied and cannot have complete access to the data to the degree that it would have if the investigator were a paid employee; hence, it cannot fully assure itself of the completeness, adequacy, and suitability of the data.

(c) Under the present system, independent investigators feel pressured to provide favorable reports to their sponsoring or contracting companies if they hope to generate future "business." However, if they were on the regular payroll, they would have no more pressure in this regard than other comparable departments within the firm, such as the other divisions within the research and development department.

(d) The clinical investigations could be made a much more intimate part of the comprehensive NDA in that they would be simply another part of the company's overall research effort rather than a separate sort of "appendage" to the NDA, as many of them are currently.

I realize that some may object to such an arrangement in that it tends to reduce "academic freedom." On the other side of the coin, however, it also tends to result in better cooperation and interchange between industry and academia—a goal or objective that we frequently hear and read is being currently encouraged. As I noted above, I am not sure this is either the preferred or even a feasible idea, but it is one alternative to our present system.

Edward G. Feldmann
American Pharmaceutical Association
Washington, DC 20037

Received June 8, 1983.

Goyan letter to Feldmann, dated June 14, 1983:

Thank you for your letter of June 7. I hope you will see fit to publish your thoughts, as outlined in the letter, in the *Journal* in the near future. They are both interesting and provocative and may well be the way of the future. In any case, you have struck a responsive chord in a number of us, and I, for one, would like to see some sort of debate initiated in this regard.

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Received June 17, 1983.

Kavanagh letter to Feldman

Your editorial "The Weak Link in New Drug Research" [1] points to an old problem well known to drug makers which is now receiving public attention. I see no way to improve the quality of clinical testing and its evaluation. My reasons are the following.

These observations are based on approximately 28 years of experience with two drug companies and rely on material provided to me by employees of other companies. In general, the opinion among scientists employed by drug companies is that physicians make very poor directors of research, at any level, since they have neither the aptitude for scientific work nor the training as scientists. My experience leads me to agree with this opinion.

A physician from Parke-Davis said in 1960 that he envied Eli Lilly and Co. because it had its own clinical facilities, in operation since 1926. This in-house clinical facility was to evaluate clinical reports submitted by outside physicians who were clinically evaluating Lilly products. The availability of this monitoring function should make clinical investigations more efficient.

Here are some specific examples. Around 1960, pediatricians in San Francisco were treating neonates routinely with 20 mg/kg chloramphenicol (twice the dose recommended by Parke-Davis for adults), and approximately one-third of the infants died. Parke-Davis, of course, was blamed. Another drug company informed me they could use only about one-third of the results from their contracted clinical studies. An analyst for another company visited six clinicians who were studying a new antibiotic and found that only one was using an assay that would give meaningful data. During the study of a new antibiotic, an assay laboratory found interfering material in the urine of patients being treated with the new antibiotic. Paper chromatography revealed as many as seven foreign antibiotics in the urine samples. The physicians were amazed that the laboratory discovered they were using more than one drug.

I wonder how much of this kind of information ever gets back to anyone in charge of clinical testing. What could be done with the

information? Obviously, this system of testing is expensive, time consuming, and frustrating for the drug companies, but what can they do as long as physicians dominate clinical testing?

The basic problem with clinical testing is the assumption that physicians are scientists. There is no reason to expect a physician to be a scientist.

Clinical testing will improve only when properly qualified people do the work. The physicians who are members of a testing team should be selected for scientific aptitude and then given the needed training. The team should include a physician, a pharmacist (preferably Pharm.D.), an experienced technical writer (to help organize data and prepare the reports), and such other support personnel as needed for that particular study. In the case of antibiotic testing, the team should include someone experienced in the principles and practices of using a microbiological assay for antibiotics (these people are rare).

One reason I am pessimistic about the possibility of improving clinical testing is the difficulty in getting physicians to give up the power they now possess. The ego problem could be minimized by selecting the physician members from among those who have a Ph.D. degree in a related subject such as zoology or physiology. Their previous experience in a laboratory would assure their understanding the importance of scientific protocol, the awareness that correlation and cause are not synonymous, and the effects of genetic makeup of the patients on results.

Many more examples could be given, but these are sufficient to indicate what some of the problems are. Obviously, no drug firm would dare make public these complaints. The firms doing the research are dependent on the good will of physicians for their success.

Frederick Kavanagh
Corvallis, Oregon 97330

Received August 9, 1983.

[1] E. G. Feldmann, *J. Pharm. Sci.*, **72**, 463 (1983).

Pharmaceutical Analysis and Control Award

Members of the Pharmaceutical Analysis and Control (PAC) Section of the APhA Academy of Pharmaceutical Sciences are concerned about the paucity of students choosing to study pharmaceutical analysis at the doctoral level. As a means of promoting graduate study in this discipline, the PAC Section is offering an undergraduate award in pharmaceutical analysis for 1984. Applications are currently being invited from undergraduate students enrolled in the last two years of baccalaureate or equivalent degree programs in accredited schools or colleges of pharmacy and departments of chemistry who have demonstrated interest and potential for a career in pharmaceutical analysis. The Award will consist of scholarship support ($1,000) for a ten-week summer period or equivalent (NLT 400 hrs) of laboratory research in pharmaceutical analysis. Applications are due in the Academy Office by December 31, 1983. Notice of awards will be mailed by March 31, 1984. Application instructions and application forms are available by calling or writing: APhA Academy of Pharmaceutical Sciences, Undergraduate Award in Pharmaceutical Analysis, 2215 Constitution Avenue, N.W., Washington, D.C., 20037, (202) 628-4410.

We encourage faculty and students to apply for the PAC Award in Pharmaceutical Analysis. Thank you.

Robert V. Smith, Ph.D.
Chairman Elect,
PAC Section, APhA Academy of Pharmaceutical Sciences

Received August 18, 1983.