Problems in Drug Development as they Relate to the Pharmaceutical Industry

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THE first question posed when discussing the effect of the new law and regulations is: "Have they improved safety?" The answer must be "yes"—but with some qualifications. The increased awareness of the possible effects of drugs on diverse organ systems and fetal development and the absolute requirement of extensive animal toxicity tests before any clinical investigation of a new drug can have no other effect but to enhance the protection of the drug-using public. Further, as noted below—at least at this time—there are fewer new drugs being introduced into general use. It follows that there is lesser opportunity for unexpected adverse reaction to such agents. The net result is, therefore, increased safety.

This assurance must of course be qualified by the fact that unsuspected reactions may still be overlooked and that species, temporal, and other variations in activity prevent absolute assurance that any new agent is "safe." I need not elaborate what these untestable dangers are, except to mention two well-known examples: at this date the rare sensitivity and similarly a leukopenic reaction can be discovered before introduction only by chance. It has seemed to many of us that a real service to science and to the public would be to calculate the odds that a new agent might in time produce these reactions when introduced into general use. For example, if 100,000 patients had been studied before the introduction of a new drug, the odds of discovering a 1 in 50,000 reaction would be a certain figure, but if only 1,000 patients had been exposed to the agent the odds would be very much greater, but could be calculated.* This is one of the reasons I do *not* believe that "wider" or Phase III trials—utilizing the general practitioner—can be abandoned.

An equally important question regarding the effect of the law and regulations on clinical research has to do with its effect upon research itself. I would like to address myself to this question from several points of view.

From the standpoint of the pharmaceutical industry there is no question but that the development of a new drug under today's conditions is a much slower and more expensive process.

To a member of the clinical research staff of a pharmaceutical manufacturer the impact of the new law and regulations has been overwhelming. The immediate and

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* It was recommended by the Subcommittee on Wider-Scale Trials on General Basis that research of a statistical and epidemiological nature be undertaken to determine how many subjects are essential to achieve meaningful results. The Committee pointed out that "it should be possible to predict how many patients will be required under varying circumstances to demonstrate each type of toxicity or side effect." Report of the Commission on Drug Safety, 1964, pp. 74, 75.

unprintable reaction reflects the enormous increase in paper work and the infinite detail that are now demanded of the individual responsible for the clinical development of a drug for a pharmaceutical manufacturer. The present insistence on supportive data for any conclusion of a clinical investigation (which means individual case reports and all details, such as all laboratory reports) makes the simple accumulation of this material, collating it, and preparing it in some sort of coherent form for review by the Food and Drug Administration a most demanding task. You have all been regaled by accounts of the size of current new drug applications. Our latest weighed 550 pounds, and is by no means a record. Sending in supplementary case data on that particular application involved reproducing, collating, and forwarding over 80,000 individual sheets of paper!

We cannot argue that the Food and Drug Administration should not have access to all supporting data for conclusions about our new drugs. On the other hand, there surely must be other ways of obtaining access to the information without requiring such quantities which must overtax the Food and Drug Administration's already over-extended facilities. I am sure the Administration feels the same way about it as do we, and there are heartening signs that steps are being taken to correct it. The Conference held in Washington on October 23rd is indicative of at least efforts to progress in this area. We can hope that some time in the future an appropriate system of transmitting data will be found practical and mutually satisfactory. One can envisage the time when we simply plug in our computer with theirs via long-distance telephone lines, and let the two electronic beasts talk to each other and eventually let us know what they had decided.

From present experience, I am sure it would be "incomplete."

I am not of course being facetious about electronic and mechanical means of transmitting necessary data. We all agree that some such system will eventually be utilized. In the meantime, it is still necessary to accumulate and classify input data no matter what system is employed. The present insistence (which may be and probably is entirely proper) upon the precise recording of *all* data, rather than the individual academic or independent investigator's formal report or publication, is still a gargantuan task and calls for the employment of rigid procedures that may be somewhat abrasive. More about this later.

The new law demands positive approval by the Food and Drug Administration of a new drug application, which means essentially certifying within specified limits the safety and efficacy of any new drug. As a result, there is a justifiable insistence upon much more data than previously required, and, quite obviously, the careful review of this tremendous mass of information takes more time.

The rewards to the Food and Drug Administration Medical Officer for approving the general distribution of an effective and useful new agent, no matter how spectacular, do not seem to have caught up with the adverse effects that could occur if he let one go by that later proved to have severe and headline-making "toxicity." With the whole world and particularly congressional investigating committees looking over his shoulder, it is no wonder he wishes to have all possible information about a new drug's activity on all organ systems, in varying age and sex populations, at multiple dosage strengths, and over extended periods of time. With this ideal we cannot argue. Nevertheless, this does pose a considerable problem to the clinical investigator in industry since it enormously increases the number of investigations he must establish for a new agent.

Our colleagues in academic circles have not been distinguished by their enthusiasm for this type of careful, repetitious investigation. One is hard put to arrange the required studies, which, if not done by fully qualified individuals (the very ones who don't want to do it), are immediately rejected or decried as not being adequate.

The new law requires "adequate and well controlled" studies, a most commendable aim. But, what is "adequate" and how controlled is "well"? In practice this should mean "enough," but it is currently almost always interpreted as "more." Letters from the Food and Drug Administration use this phrase almost as if building a legal defense, not a scientific argument. Also, there are controls and controls, and the ritual dance of the double-blind is not universally applicable. Dr. Sadusk's recent discussion of the subject, listing the conditions under which the double-blind technique could or should be unnecessary, is reassuring although still allowing very great individuality of interpretation. Further, the role and competence of the industry clinical investigator, who may in large part share in the careful design of such "open" studies, does not seem to be acknowledged. Again, I find Dr. Sadusk's earlier reported comment that there were "only" four well controlled studies on Parnate disquieting. If "well controlled," four *should* be more than "adequate."

Another feature of new drug development today was with us under the old law but has been considerably magnified by the enormous increase in workload imposed on the Food and Drug Administration by the new law and regulations. Of all of the various factors that give the industrial clinical investigator a sense of absolute frustration, the "incomplete filing" maneuver (which seems to be a standard practice, and for that matter was so before Kefauver) heads the list. Don't mistake me, I am not necessarily criticizing the decision that a given application is "incomplete." Obviously my own department (and I am sure those of our competitors) has always been convinced that the application *was* complete or we wouldn't have bothered to submit it. One certainly can recognize honest differences of opinion and the fact that one can be so close to the forest that he can't see the trees. What we do hope for, however, is that eventually, given adequate help, time to catch up, or what have you, at least a preliminary review of a new drug application could be made shortly after submission, and any obvious omissions or inadequacies called to the attention of the sponsor immediately. As it stands today, such notice is given only after the 180 days prescribed by the regulations have almost passed. If one assumes that at least three months are spent in assembling the accumulating data on a new drug application—perhaps other departments can do better, but that's certainly speedy work for mine!—this means that nine months have elapsed from the time a summary is made until the "incomplete" ax falls. It is not easy to go back and pick up the pieces nine months later with any degree of continuity. It may be necessary to initiate or reinstitute an involved program which of course adds months to the development of a new drug. If that drug has value, such delay is not serving the public.

In any event, the net result is a considerable increase in the amount of detailed work and paper shuffling which the manufacturer's agent has to undertake, a considerable increase in his budgetary expenses, and a slower release of new drugs to the public. This poses a further problem. Management has some difficulty in understanding why, with all the increased help and increased budget that provided the painfully and slowly accumulated data necessary for a new drug application, it should take so long to "get approval." On the other hand, the Food

and Drug Administration asks for more and more data. This means more and more personnel, more and more money, and more and more time. Being in this particular middle is not the result of the new law since it has existed at least since 1938. But the new law and regulations have infinitely increased the proportions of this particular Scylla and Charybdis.

With all due respect for other opinion, I do not believe that the academic or independent clinical investigator has really felt the full impact of the new regulations yet. True enough, he has filled out his share of forms 1572 and 1573. But these are relatively simple, since everyone has a copy of his curriculum vitae, and if he hasn't prepared a written outline of his experimental design, he certainly should (or the "sponsor" will do it for him). Also a number have gone through the "you be your own sponsor" routine for the compound that the manufacturer does not wish to or cannot sponsor. It has seemed to me that at least a certain number of independent investigators have felt that our refusal to sponsor an IND for a drug for the single patient, or for the particularly interested investigator, or for "courtesy," has been due to our own disinclination to spend money or time, or just simple lack of understanding of the principles of research. Nevertheless these irritations are minor compared to those I see ahead.

I noted above that there is an increasing and inflexible interest in collecting *all* data pertaining to new drug investigations. Further, I observed that we could not really quarrel with the fact that these data should be available for inspection, however it might be ultimately handled. This does, however, imply that all data pertaining to all patients treated with an investigational drug must be made available and reported by the independent investigator. We have found this almost impossible to achieve, and I believe our experience will be affirmed by my colleagues in the industry. We are currently going through our own agonizing reappraisal, and foresee that we will of necessity divide our clinical investigations into two different groups. In one will be the investigator who has the time, equipment, training, and all the rest, to design, carry through, and submit an adequate report of his investigation on demand, and *who will agree to make available full supporting data covering his formal report, also on demand.* In the other group will be those who, however capable of preparing their own experimental design, see the virtues of accepting a predetermined design prepared by ourselves and a data handling scheme which necessitates a prepared case report form designed to fit our own data handling procedures.

For the first group, we really face the "agonizing reappraisal." We have spent our professional lifetime making the acquaintance and obtaining the co-operative effort of a great many fully qualified investigators who are quite competent to do all of the things outlined above. Not all of them, however, are willing to produce full and complete data on schedule. We have made efforts to send our own people into those laboratories to extract the necessary information; this has been partially successful but not entirely so. We are faced with the decision of either sending in our own full-time data collecting team of each of these investigators (if he will stand for it!) or terminating our relationship; the new regulations leave us no other course for *the drug may not be supplied to investigators who repeatedly or deliberately fail to maintain or make available required records or reports.*

This may not be much of a hardship for some since "drug testing" is not really socially acceptable in many quarters, especially now with the National Institutes of Health just around the corner. It *will* mean that some of our best investigators,

with the most independent minds, will probably not be available for the careful evaluation of all aspects of a new drug's activity, which all agree is very much worthwhile (and in any event is now a fixed requirement).

It will also mean the increasing standardization of clinical investigation, with an inevitable preponderance of rigid adherence to predetermined design and protocol, proceeding inexorably to a prescribed end, with great difficulties put in the way of the spontaneous flight of fancy that might conceivably lead to valuable discovery.

I do believe in mass data and the epidemiological approach to drug effects. At least at the moment the only way I can see to utilize that approach is to further standardize the procedures mentioned above. Nevertheless, the prospect of the extension (and I am being totally realistic) of our conversing computers to a programmed data-receiving unit in each clinic and hospital ward, into which specific patient data are fed, matched against a template, and rejected for further information or, if complete, sent on to our machines, here to be correlated with similar data coming from other patient centers, and then forwarded to the Big Brother machine in Washington (with its probable answer "incomplete") is a little grim.

Nonetheless, this seems technically feasible, if financially impractical at the present time, and some such system might very well evolve rather rapidly.

As a result of all this there is a growing effort on the part of the Clinical Research Departments of various manufacturers either to establish their own hospital ward system (as Lilly has done) or a 100 per cent industry operated investigational unit, such as that set up by Upjohn and Parke Davis within the Michigan prison system. One may anticipate more efforts of this sort which will be tremendously expensive and will therefore not be available to all manufacturers, and will not reduce the price of drugs.

In addition, there are developing an increasing number of "Foundations" (usually, we assume, nonprofit) who will undertake to carry out these extended clinical tolerance studies on contract. Some of these I know from personal experience to be under unimpeachable control, excellent and above reproach, but I can't help feeling a little uneasy about such developments which are quite outside the traditional concept of the responsible institutional control of clinical investigation.

I don't say that the day of the independent investigator in clinical pharmacology is over, but he is certainly having difficulties put in his way.

Incidentally, I believe that this is the year when the regulations strike home to the individual investigator. I do not know whether Food and Drug Administration inspectors have yet visited clinical pharmacologists or not, but they certainly have gone through the files of various pharmaceutical manufacturers, including ours, as is their right and duty under the new law and regulations. Such inspections as we have had have been invariably polite and well-mannered. Still, the insistence upon individual case record data and the individual aberrant reaction (including minor transient decreases in systolic blood pressure seen in the day-to-day observation of a single one of a whole series of patients receiving a drug which has no known effect upon cardiac output or peripheral resistance) is disturbing in the implication that it is *really* intended that every single bit of evidence on every patient who ever receives an experimental drug must be coded and made available. In the instance cited above, and others, the requirement of specifically commenting on each such occurrence, not only to the Food and Drug Administration but to

other clinical investigators studying the same drug, was laid down. I hope that such bemusement with minor variations in a labile homeostatic mechanism reflects inexperience that will quickly become considerably more sophisticated. Nonetheless, I do want to impress upon you that every single bit of data on patients treated by you with an experimental drug is not your own. It belongs to the Government.

What have the new drug law and regulations meant to the public? As mentioned above, I believe the public is receiving greater safety insofar as untoward effects to new drugs are concerned. On the other hand, they are temporarily, at least, paying for it by having fewer new drugs. That this is not considered to be a calamity by all I well recognize. Nonetheless, there are unquestionably some individuals who are not as well off without that unknown new drug as they would be if the drug were available. It is also true that they don't know it, whereas they do know there is some measure of reassurance that "drugs are safer."

I believe that the public (and the profession for that matter) should become much more aware of the "risk to benefit" balance which must be struck with respect to any new drug or for any new treatment or any new advance of any sort. "Safety" is always a relative term and biologic bookkeeping of this kind should be done on an epidemiologic basis and be much more widely publicized than it is now. It is all very well for the profession and the public to be alert to and alarmed at drug reactions, and to do everything in their power to keep these at a minimum. Nevertheless, to me (and remember I am biased) the pendulum has swung much too far in the other direction, to the extent that many individual members of the public, to my personal knowledge, are more concerned about nonexistent reactions than they are with the evident benefit they have obtained from the drug they are taking.

I also subscribe to the worth and desirability of the many efforts to establish and correlate drug reaction reporting systems, both here and abroad. Nevertheless, I think it must be thoroughly understood by all, including the public, that these early alert systems are just that and should not be accepted as anything else. I am sure you all agree that the principles of control must be applied to determining whether a drug really has caused a "reaction" or not, just as much as they are to the probability that a drug produces a beneficial effect.

I should like to conclude by placing before the members of this College a plea that they accept their responsibility in the situation I have attempted to describe. I believe very strongly that independent, nongovernmental organizations, such as this College, have a demanding role to play. I would like to suggest that such organizations establish an active reviewing function, perhaps even by forming standing committees on specific subjects. As subjects for review—*not* simply criticism (both the Food and Drug Administration and the industry have adequate facilities for that!)—I suggest the following:

1. The nature and extent of the animal toxicity data required prior to the clinical investigation of a drug.

2. The nature and extent of the clinical evidence required to prove "safety and efficacy."

3. Above all, the means to arouse the scientific community to an appreciation of the necessity of their personal participation in the necessary, complex and repetitive studies on drug activity and toxicity. Without such an impartial and constructive review the independent investigator will, in my opinion, have been derelict in his duty.

And finally, I submit that the properly qualified industry scientist has every right to membership in these reviewing bodies.