Clinical Trials and the Drug Review Process

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I would like to express my appreciation to the American College of Chest Physicians for inviting me to join you here today, to discuss certain issues bearing on the Food and Drug Administration and its performance. Certainly, we have many things to discuss.

For example, of all I heard about the so-called "drug lag" when I was in Washington, I heard most about beclomethasone and the apparent slowness with which that drug appeared on the American market. While to many of you the FDA may have seemed somewhat defensive about the "drug lag," the Agency, and I as part of it, felt somewhat ill-used and put-upon by a good bit of what has been said on this subject. The ingredients of the "drug lag" issue include not only that some drugs appear in the United Kingdom or other countries before they are marketed in the US, but also that drug research and production are moving overseas, that drug research is being slowed down, that drug research is becoming too expensive to do, and that the cost/benefit ratio of the new drug regulatory process has gotten too high. The blame for all of this is usually laid directly on FDA's doorstep. No one talks about the costs of labor, equipment or construction in this country as opposed to countries overseas. No one talks about our high ethical standards or our requirement for Institutional Review Committees, or the many rules for protecting our experimental subjects. The only apparent concern is over FDA's regulations and FDA's alleged reluctance to accept the results of less than perfect clinical trials.

But I have heard few people ever ask why FDA behaves as it does—whether FDA's rules and regulations faithfully reflect the mandates of the Food, Drug and Cosmetic Act, or are really FDA's arbitrary extension of authority it doesn't legally possess. As the person who ultimately has been responsible for FDA's policies and behavior during the past few years, I welcome this opportunity to try to explain what we have been trying to do with the new drug review process. I will pay particular regard to clinical trials, to our guidelines for clinical trials, the meaning of these guidelines, and the importance of clinical trials to the new drug approval process.

I hope I might be excused for having some strong feelings about these subjects—feelings developed to some extent by my scientific training, but fixed by dozens of appearances before Congressional committees. If you read newspapers, you must know that FDA, with increasing frequency, is hauled before Congress to explain some misadventure with one or another drug. I wince inwardly as I recall some of these painful experiences. As I refresh your memories by reciting a short list, consider the relationship of the problems to the controlled clinical trial.

Early in my career as Commissioner came the Dalkon Shield controversy and the resulting Congressional hearings, which ended only with the disappearance of this intrauterine device. Was it really less safe or less effective than others, more safe and effective, or the same? There were no trials, so no one will ever know, with certainty. Next, I recall chymopapain, the enzyme injected into ruptured intervertebral disks. No controlled trials had been done, although FDA had reports of 10,000 cases done in this country. When a good placebo-controlled study was done just as we were about to approve the drug, we learned that chymopapain and the placebo control were equally effective—or equally ineffective.

Repeated Congressional hearings have explored whether the oral hypoglycemic agents should remain on the market. Central to this decision is the design and control of the UGDP study. We discussed with Congress whether the amphetamines are effective for treating obesity; whether propranolol was actually responsible for the lessening of angina pectoris; whether Flagyl was too toxic; whether estrogens were safe and effective as contraceptives—either before or after intercourse, and on and on.

In each case, the questions arose around issues resolvable by properly randomized, properly controlled, well performed clinical tests. Thus, the strength of some of my feelings.

Many people tend to forget, or don't know, that the various steps in the new drug approval process are not actually under the direct control of FDA. In fact, until fairly recently, FDA mostly has reacted to what was submitted to it by drug sponsors—principally pharmaceutical houses. As was the case with beclomethasone for a time, the FDA obviously is unable to consider approving a drug if no new drug...
application has been submitted. With our present system, a drug sponsor first applies for an Investigational New Drug Exemption (IND), and later submits his New Drug Application (NDA), thereby supplying to the Food and Drug Administration the results of his animal studies and human investigations. The drug sponsor traditionally has chosen the type of studies to be done, has dictated the design of the study and has been responsible for the quality of the work, no matter who did it. The sponsor has analyzed his results, drawn conclusions therefrom and submitted all his material to the FDA. Therefore, the principal factors governing FDA’s response to any new drug application have been the timing of the receipt of the information, and the quality of the data supplied. All too often, drug approvals have been slowed, either because required material has come in slowly, or because data submitted have been unbelievable, unreliable, insufficient or irrelevant to the important questions asked by FDA.

But FDA critics have charged that FDA has dragged its feet when evaluating data submitted, that FDA requirements for research (particularly clinical trials) have not been made clear, and that FDA’s regulations and requirements have, in fact, been arbitrary, if not capricious. Most common is the feeling that FDA’s rules are too strict. The place one must begin examining these charges is the Food, Drug, and Cosmetic Act, in which Congress has told FDA what to do. The new drug section of the F, D & C Act is Section 505; it is instructive to hear what the law mandates. Here is a brief summary, in the words of the Act. The new drug application must consist of six parts:

1. Full reports of investigations of safety and effectiveness.
2. Full listing of the components of the drug.
3. A full statement of the composition of the drug.
4. A full description of the methods, facilities and controls used for the manufacturing, processing and packing of the drug.
5. Samples of the drug.

Sub-section D of Section 505 lists the reasons a new drug application shall be disapproved (following a hearing). These reasons are:

1. If the investigations done are not adequate tests, and do not represent all methods reasonably applicable to the determination of safety.
2. If the drug is found unsafe; or, conversely, is not shown to be safe.
3. The methods, facilities and controls used to manufacture, process and pack the drug are inadequate.
4. The information submitted, or any other information, is insufficient to determine safety of the drug’s use.
5. The information submitted, or any other information is insufficient to determine effectiveness of the drug.
6. The labeling is evaluated as false or misleading in any particular.

Now, when the strictness of the new drug sections of FDA’s regulations is judged, it must be done in light of what FDA has been ordered by Congress to do. And note the careful emphasis in the law on completeness, thoroughness, comprehensiveness: “All methods of research reasonably applicable,” “Full reports,” “Full listing,” “Full statements,” “Full description,” “False or misleading in any particular.”

I can assure you that to anyone given the responsibility for enforcing this law, it is obvious that the standards set in the law are high, and that these high standards must be reflected in FDA’s regulations. Furthermore, as I have learned through repeated experience, if one is asked by a Congressional committee why a particular drug was approved, and then told that in the view of the lawmakers, the approval was improper or even illegal, then one quickly learns to interpret the law and to write regulations with great care and a degree of strictness.

The practical results of all this have been both good and bad. There is no question in my mind that our drug supply is the safest in the world, and that FDA has exercised commendable caution in carrying out its responsibility to protect the American consumer. The other side of the coin is that the judgments FDA must make are extremely difficult and complex, and often have to be made in the absence of definitive data of one kind or another.

It has long been my view that FDA could be fairly criticized for two specific aspects of how it went about the new drug review process. First, given the high standards of the F D & C Act, the criteria by which FDA judges what is “All reasonable methods of research,” what is a “Full report,” what is a “Full description” of something, are of paramount importance. But no one outside the Agency has known what the criteria are. I can well understand the frustration and anger of a drug sponsor or its research team if the immense amount of work to complete an NDA was done, and only then was it learned that FDA did not think the research adequate or the reports abundant enough. And, if the drug sponsor was unable to find out what the Agency did consider to be adequate or abundant, the drug sponsor could be forgiven for wanting to repeal the Food, Drug and Cosmetic Act, lynch the Com-
missioner, or both. Second, the judgments made by FDA are often of a type difficult for anyone to make, and they would be impossible to understand in the absence of personal knowledge of how the judgments were made and the scientific basis on which they were made.

In the past few years, including those just before I joined the Agency, FDA has come a long way toward resolving those two particular problems. FDA's answer has been to try to "institutionalize" the new drug review process by adopting a team approach to the evaluation of INDs and NDAs. A medical officer, a chemist, a pharmacologist, and others appropriate to a particular drug category, are assigned as a review team. This team of specialists is able to share its experience, expertise and opinion. Also, the Agency has been very aggressive in establishing and using advisory committees composed of the best experts to be found in this and often in other countries. The advisory committees have been assigned to categories of drugs, and have begun to work directly with our staff teams, the goal being for everyone to know, trust, like and help each other do the difficult work of FDA. The advisory committees and our staff have been working together to set standards and criteria that reflect the law, to help explain those standards and criteria to drug sponsors and scientists, to help FDA apply those standards to scientific work done, and to advise FDA as to whether or not the standards are, in fact, being met. During the past few months, all advisory committee meetings have been open to the public, except for those portions of certain meetings that had, by law, to be closed. This step has allowed a much wider participation in FDA's process of decision-making, and certainly has fostered a better understanding of FDA's decisions, and why and how they have been made.

It has been, and will continue to be, Agency policy to demand adequate and well controlled investigations, including clinical trials, done by experts qualified by their scientific training and experience to do the work and to evaluate it. This policy has been challenged as being an example of FDA's arbitrary extension of its authority. But, in fact, the policy I just stated is a direct quote from the Food, Drug and Cosmetic Act. The standard of adequate and well controlled clinical trials done by qualified experts comes directly from the nation's law. It is my view that the number of properly controlled clinical trials done in this country is far too few, rather than too many. I believe it far less costly in the long run to know the truth from clinical trials, than to make a judgment, or to guess at the truth, based on inferior data.

Further, it has been the policy of the agency to insist upon controlled trials when controls are feasible, randomization of subjects when that is at all possible, and for the trial to be blinded when this is feasible. The rub, of course, comes in deciding what is really possible or feasible, in any given circumstance.

I have now, of course, got to the interesting question of the meaning of, and the proper degree of specificity of guidelines for clinical trials. Guidelines are simply strong suggestions, and not invariable rules. I think everyone can understand that. Yet, I noted in reviewing advisory committee discussions about the guidelines for clinical testing of bronchodilator drugs that fears were expressed, to quote a member of the advisory committee, that the "guidelines would become gospel." And because of this concern, the guidelines were, in places, made quite general and nonspecific. I believe that in becoming less specific, they became of less practical value.

It is my strong belief that guidelines for clinical trials should be detailed and specific, and should speak directly to the purposes of the trial, the design and conduct of the study, the methods of study experts consider adequate, and even the recommended ways to handle data. If guidelines for clinical trials are made comprehensive and complete, they will then be of maximum use in upgrading the quality of the research done in the drug field, and that is a desirable outcome. And if a scientist wishes to do otherwise than suggested by the guidelines, he or she obviously can, and this should be made clear in the guidelines. But the guidelines should be explicit about what experts believe to be best. The scientist who does something else is obligated to know why he or she is straying from the guidelines, and should so state in the research protocol.

If guidelines state only that controls should be "adequate," without defining what type of controls experts believe to be possible and desirable and thus adequate in that circumstance, then the guidelines really aren't as useful as they ought to be. And I would remind you of a point I made earlier. In a real sense, guidelines for clinical trials are criteria for FDA decision-making. Thus, the more specific you are in framing these guidelines, the more impact you are having on FDA's decisions about new drugs.

I will comment briefly on one other aspect of guidelines for clinical research. FDA has learned from recent experience something most scientists know, but forget—the importance of placebo control. Our experience with chymopapain demonstrated that at times it is far more ethical, not to mention scientific, to use a placebo control than to try to avoid it in the belief that placebo therapy of an
illness is unethical. And the same goes for the use of a similar, proven effective drug as a second type of control. It is foolish, and will prove shortsighted, to try to avoid the use of such controls.

The weakest part of our knowledge about the proper use of drugs concerns the post-approval period—the longterm safety and effectiveness of drugs, the incidence and kinds of adverse drug reactions, drug-drug interactions, and the effect of drugs on pregnant women and children. In the future, clinical trials will have to be so designed that these questions can be answered. This will obviously require that clinical trials become longer in duration, larger in size, and more complex. I would guess that in the future, FDA will be asked by Congress to judge the relative safety, and the relative effectiveness, of groups of drugs. FDA does this now, to some extent, as with the sequential contraceptives, which were removed from the market as less safe and less effective than the standard "pill." But FDA's making such judgments will force clinical trials to be larger, longer and more numerous.

In this overview of a very large subject I have tried to impress upon you that FDA has changed how it goes about the drug review process. FDA is opening up its procedures; it is going public. FDA is inviting you to participate, to become a part of the system. I believe that FDA has become very responsive to people who know how to approach the Agency, and to people who are willing to do so. In short, in the future, if you are very unhappy with what FDA is doing with drugs in your field, it will, at least in part, be your fault. It is difficult for individual physicians to become involved with FDA. But when individuals don't have the time or the ability to accomplish something, they can organize to do so. The American College of Chest Physicians provides one such means of working with FDA.

DISCUSSION

Dr. Rachelefsky: Is there a procedure whereby the FDA can share experiences with other countries in order to save time, expense and to add to the comprehensiveness of evaluation of drugs?

Dr. Schmidt: We do some sharing of data now, but probably not enough. A number of people have argued that since many drugs now are developed in other countries, the FDA should accept the results of the studies done in other countries. The FDA has recently begun accepting clinical trial data and some other kinds of data from foreign countries under certain defined circumstances. For example, the studies must be well designed, and they must be done under the conditions of the Declaration of Helsinki. We find too few clinical trials done overseas that are acceptable scientifically or ethically in this country.

Dr. Biorman: I was on a Committee of the American Academy of Pediatrics that made four recommendations to you in November, 1974. We recommended that pediatric studies of new drugs should begin when Phase III adult studies were getting underway. The second principal was an obvious one, that studies should begin with older children and work back to the younger. The third recommendation was that placebo controls were immoral if an effective drug existed for the condition, and finally, that there should be a long-term pediatric Phase IV study to assess effects of the drug on growth and development if the drug was going to be used chronically in children. Do you have any comment?

Dr. Schmidt: The language of the various legislative revisions of the drug laws being considered by Congress will likely preclude studies on children or pregnant women until at least Phase III studies are complete in adults. To telescope the process and allow the initiation of studies in older children on the basis of Phase II and early Phase III information in adults could be done, but probably won't be until judgments about the safety of so doing can be made by experts in public. Ideally, everyone should know what is being done and why it is being done, before it is done. This type of public disclosure of safety and effectiveness data will answer many questions, and prevent the Commissioner of Food and Drugs and the Director of the Bureau of Drugs from being called up before Congress to explain why they are subjecting pregnant women and children to great risks and unethical research, etc. I agree with the recommendations made by the American Academy of Pediatrics, but the Agency has not yet found a way to carry them out.

Dr. McPhillips: Is industry represented on the committee of experts that draw up the guidelines? If not, do you think they should be?

Dr. Schmidt: There are industry scientists on some of our advisory committees. It depends upon the purpose of the committee. For the OTC drug review panels, there is an industry representative and a consumer representative on every panel. The obvious problem is that industry representatives may have a conflict of interest very frequently. The conflict of interest provisions and the secrecy provisions of the law have caused us to be cautious about industry representatives on our committees. Technical advisory committees are supposed to make scientific decisions, and FDA wants the best scientists to serve. If they happen to be in industry and they are on our advisory committees, they are there as scientists, not as representatives of industry. Since the committees now meet in open session, there is adequate opportunity for industry, consumerists and anybody else to address these committees.

Dr. Fellers: What allowances can be made for the exceptional patient, for the individual who only responds to a certain drug or only experiences side effects from a certain drug?

Dr. Schmidt: There is now some thought being given by Congress to change the drug laws such that FDA would designate more specifically the allowable uses for drugs. According to this idea, the FDA would state on
the label the conditions for which physicians could legally use a particular drug. Very toxic drugs, and drugs not yet proved safe or effective for long-term use would be available only in certain circumstances, or to certain qualified physicians. The underlying issue here is whether we are trying to protect 90, or 97, or 100 percent of the public. The difference in the answers makes a big difference in what drugs one can allow on the market and how freely they can be used.

The ideas for greater restrictions on drug usage come from our present experience relating to overuse and misuse of toxic drugs. One of my greatest problems as Commissioner was the ease with which Congress could demonstrate in open hearings how many drugs were misused and overused in this country by physicians. Clindomycin and lincomycin are examples of drugs that are too frequently used, have serious and even lethal side effects, and are needed by a relatively small percentage of those for whom it is now prescribed. Phenformin is another example. Theoretically, that drug could remain legally available for those who really need it, but would not be available for the run-of-the-mill patient for whom it is essentially contraindicated.

In the future, the drug review process in this country is not likely to become simpler or easier, but more complex.