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"Optimizing the Interaction Between the Food and Drug Administration and the Industry"

"The Need for Cooperation for the Public Good"

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It is a pleasure for me to be a speaker at this conference, to share the podium with a friend and former colleague, Merve Schumate, of the FDA and also to have the opportunity to appear for the first time with Dr. Papariello of Wyeth Laboratories. The title for this morning's session, "Optimizing the Interaction Between the Food and Drug Administration and the Industry", is an interesting one. As I was preparing my remarks, I wondered if they would be different if I was giving this talk to an FDA seminar at the agency or at the Public Citizen Litigation Group, Nader's organization. If I was talking to Dr. Sidney Wolf of the Litigation Group, I'm sure that his optimization plan between FDA and the Industry would be tied to the concept of having open files, everything in writing and memoranda for all meetings. I feel fairly certain that Dr. Wolf would wish to have the opportunity to have either himself or one of his colleagues attend any of the meetings that they thought worthy of their time and effort. Now if I was an FDA reviewer and was talking about optimizing the interaction, I would see Industry representatives submitting well researched NDA files and supplements. These Industry representives would quickly understand and appreciate the wisdom of my request for additional studies, more data for the NDA, and the use of certain terms and concepts in relationship to labeling and promotional activities. They would find my suggestion of a patient package insert to be extremely helpful. On the other hand, if I were to become one of Dr. Papariello's researchers, I'm sure that I would see optimization of the system occur when my explanation to the FDA reviewer was quickly understood, all my views on the relationship of the data to the study submitted were accepted without question, and the agency looked most favorably on everything that was submitted to support the application.

Having concluded that the views from these three described perspectives were unrealistic, I decided that what we really want to talk about is promoting interaction between the FDA and the Industry.

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Optimization should occur for the consuming public who buys the drugs that are made by the manufacturer and who, through taxes, pays the salaries of the FDA employess who are charged with reviewing and approving the drugs prior to their marketing. The public consumer wants a system that allows a drug to enter the market as soon as possible so that he or she may have it available through their physician anytime they become ill. At the same time they want the drug to be as safe and effective as possible, and they want the reviewer at the FDA to be careful in approving the drug. Finally, they want a marketing effort that informs the doctor of the advantages and side effects.

Obviously, the individual public citizen cannot have a serious impact on FDA, so we really need to look at who speaks for the public. Let us reflect back for a minute and remember that the beginning of the regulation of drugs actually occured in 1902 with the Virus Act. (1) This statute placed responsiblity on the Public Health Service to guarantee the safety of viruses that were supplied to the public. It was followed in 1906 by the Pure Food and Drug Act which was, at the time, primiarly concerned with adulterated and misbranded foods. There were in 1906 a number of patent medicines of questionable safety, but the real driving force behind the passage of the 1906 Act was Upton Sinclair's book, The Jungle, which discussed the deplorable conditions in the Chicago stock yards. Under the 1906 Act the FDA had the authority to seize a misbranded or adulterated drug and remove it from the market, but there was no preclearance system. The manufacturer did not need to come to FDA and say that they were planning on marketing a particular drug.

In 1938 a new Food and Drug Act (3) was passed replacing the 1906 Act. At that time, a pharmaceutical firm in Tennessee had as its chief researcher a pharmacist named Watkins. The wonder compounds of the day were sulfa. As you all know, sulfa is not a product that dissolves in water, therefore, there was not a pediatric dosage form of sulfa available to the physician. Mr. Watkins, during some experiments, mixed sulfanilamide with a vehicle and came up with an excellent pharmaceutical preparation. The sulfa readily dissolved, gave good color, was completly mixed and the taste was fine. The taste test was done by placing some on the end of the tongue. The firm rushed to market with this new wonderful Elixir without doing any toxicology testing. Unfortunately, the vehicle for the sulfanilamide was diethylene glycol, which is more readily known as anti-freeze. Diethylene glycol will destroy the kidney, and consequently a number of people who received the product died. The passage of the 1938 Act quickly followed. It requires any manufacturer who was introducing a "new drug" into the market place to prove to the FDA that the product was safe. The manufacturer needed only to submit the data and give the FDA time to notify if it had any problems. The burden was on the FDA to tell the manufacturer not to go to market. If the FDA failed to do anything, then the manufacturer was permitted to market its drug.

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1 Public Law No. 57-244, 32 Stat 728 (1902)
2 Public Law No. 59-386, 34 Stat 768 (1906)
3 Public Law No. 717-675, 52 Stat 1041 (1938)

The 1938 Act was not amended until 1962 when another drug was marketed which caused serious side effects. Thalidomide was marketed in Europe as an extremely safe, and also effective sleep-aid. The FDA reviewer doubted the safety of the drug, however, so the manufacturer was delayed in marketing the products in the U.S. During this delay it was learned that Thalidomide caused phocomelia, a birth defect in which children are born with flipper-like limbs instead of normal arms and legs. In reaction to this tragedy, Congress passed the 1962 drug amendments (4) which required that a new drug be not only "safe" but also "effective".

Since that time we have seen Congress acting as a watchdog, reviewing agency and industy decision making in relationship to the role of new drug approvals. Recent reviews include the drugs Oraflex, Selacryn, and E-ferol. Because the American public demands a system built on safety almost every congressional hearing held on drug approval has focused on whether the FDA has exercised the proper amount of care and overview in relationship too safety before approving a drug. Seldom, if ever, has the agency been charged with moving to slowly. The FDA, through the Congressional oversight system, is not charged with putting more drugs in the market, but with guaranteeing the safety of those that are there.

Recognizing that the FDA is charged with guaranteeing the safety of drugs, not with putting drugs in the market place, let us go back and examine for a few minutes the four basic premises that were used by the organizers of this particular meeting. In describing the issues for this session, the first is that the development, production and marketing of pharmaceutical products is influenced to a substantial degree by the Food and Drug Administration. I, for one, find that premise only partially correct. The manufacturer still determines what drugs are to be developed and clearly the manufacturer has significant control over production and marketing. It is true it would be advantageous to choose to develop drugs which the agency views as break-through drugs, because such drugs would be subject to the fast-track review process of FDA, and it is also true that the agency has certain biases in relationship to types of products. Trying to get an approval for a drug that reduces wrinkles would no doubt be a difficult process. The bottom line is the manufacturer is still "in charge" in relationship to the development, production and to marketing of pharmaceutical products. That decision is not influenced by a substantial degree by the Food and Drug Administration.

The second question is how much regulation is desirable or necessary. I have spent a few minutes discussing the evolution of the regulatory system from 1906 to the present and I would suggest to you that, with a congressional oversight group that includes a number of Senators and Congressmen interested in food and drug matters, the by-word in relationship to the drug approval process today is, as it has been for a number of years, "safety first". The FDA can cut no corners in looking at the question of safety. In fact, with a Republican White House and a Democratic House, I would suggest to you that the agency needs to be even more careful in its review process.

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4 Public Law No. 87-781, 76 Stat 796 (1962)

The third question relates to the perception that there is regulatory inequivalence between large and small firms. I would probably readily agree that if you track the approval process between large and small firms, you would find that large firms were able to get their approvals quicker. However, I would suggest to you that it has little to do with the FDA and absolutely nothing to do with bias. I think that the large firms, because of their size and man power allocation, have people who are extremely familiar with the FDA and the issues and concerns of the agency. The smaller firms because of their limited budgets, cannot afford the same type of expertise and knowledge and through oversight and mistakes may find themselves disadvantaged in relationship to the approval process. The FDA has tried, however, to respond to that problem by setting up small business manufacturing offices at a number of its regional offices. We have also seen Congress address this particular issue. The Drug Price Competition and Patent Term Restoration Act passed this last term was clearly an attempt by Congress to put the FDA in the business of not only approving safe drugs, but also assuring the American consumer that there would be less expensive drugs in the market place. This new legislation is really asking FDA to conduct economic regulation because the major safety and effectiveness issues were reviewed in the original NDA. This is a new task for FDA because it has never been asked in its prior activities to consider economic issues.

The fourth premise listed was the concept that a new drug was approved faster in western Europe than in the United States. That does not reflect well on the FDA or on the Industry's U.S. research. I think we need to look for a moment at the fact that many western European pharmaceutical firms are wholly or partially owned by their governments and that the regulatory system in many of the European countries is not as antagonistic as it is in the United States. One must also recognize that the diversity of citizenship is smaller and easier to monitor. If the FDA could approve the marketing of drugs for one small segment of the United States while it monitored the drug carefully, then you would have an agency that would be much better prepared to approve drugs in a shorter period of time than is now required.

There is one premise which was not listed in the program brochure, but which I believe may have a significant impact on the drug approval process. Some people have characterized it as controlling the bureaucracy, while others have called it the politicalization of FDA. Starting with Secretary Califano under President Carter and continuing through today, more and more decisions are being made "downtown", by the Health and Human Service staff. As increasing numbers of these decisions are made at this top level, more of the drug approval decisions will also require a closer review. Review, no matter how well planned, takes time, and time is money to the industry. Clearly a number of the industry people sought an HHS overview function because FDA seemed unresponsive to their needs. Now that the review system is being put in place, it will be interesting to see how effective it can be, or whether it will become a bottle neck in the future.

I am sure that if we spent some time, we could cite some instances where it has been helpful to have HHS overview and others where it has not been helpful. I cannot suggest to you today that this

politicalization issue has an answer, but I will suggest that you must be aware that much of FDA's decision making authority has been officially, such as the signing of Federal register notices, and unoffically transferred to HHS. Guiding an NDA through the process in the future may require approval by different people than it has in the past, and they may be asking different questions. New topics to be considered may include benefits to hospital cost containment, approval in other countries and the role of new technology. These are significant questions, but much more policy directed than those you have responded to in the past. Only time will tell what benefit HHS's overview will bring

So, after looking at these issues, we might conclude that; Industry still chooses where it wishes to go in relationship to its drug development; the agency will continue to be guided by a safety first concept; the larger firm will probably attain an approval faster than a smaller firm, and; it will probably be easier to obtain approval in Western Europe than it is in the United States.

If these statements are true, then what advantage can the public see in optimizing the interaction between the FDA and the Industry? Clearly the recent NDA Rewrite, which was finalized as a regulation on February 22 of this year, was an attempt by the agency to open lines of communication with the Industry in relationship to the drug approval process. Both the Industry and the FDA are seeking a system that provides the public and the medical profession with new drugs as quickly as posssible. The Industry must recognize that the quality of its submissions must continue to improve as new and more difficult questions are being asked. FDA commissiononer, Dr. Frank Young, has indicated that the agency is attempting, through the NDA Rewrite, to "move into the twenty-first century" in relationship to the drug approval process and to focus on the questions and issues that are important in relationship to final approval of a drug. Probably the greate step forward at this time is the setting aside of the concept that the FDA and the Industry are not working together to provide safer and more effective drugs. The new NDA Rewrite suggests that the agency is seeking to do everything it can to reduce the bureaucratic "I" dotting and "T" crossing that had begun to creep into the system. By the same token, if the "I" dotting and "T" crossing is not the main focus of the review, the data which Industry submits must not only be accurate, but must also reflect the premise that the Industry argues in relationship to the drug approval process.

A few weeks ago I heard a presentation in which the speaker suggested that the answers to the problems were not easy, but the only hope that existed was for both sides to talk. I would suggest to you today that optimizing the interaction between the Food and Drug Administration and the Industry is indeed a difficult process and that the only way such optimization can occur is for the scientists not the lawyers, nor the center heads, nor the vice presidents of marketing, but the scientists to talk about the issues and discuss the problems. Hopefully they are already talking and would find my remarks reflective of what they are already doing.