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Threats to Safe (and Effective) FDA Regulation of Products

It is now more than 27 years since I left the comforts of a more traditional career doing research at NIH to start Public Citizen's Health Research Group with Ralph Nader. Well over 60% of my time and that of my colleagues has been devoted to monitoring the FDA's oversight of the industries which it is legally obligated to regulate. Our organization has been a prominent critic of the agency, successfully petitioning and, when necessary, suing the FDA to ban or relabel a large number of drugs, medical devices, food additives or foods when, in our assessment, the scientific evidence mandates such actions.

The exciting but worrisome growth of biotechnology and the greatly increased demands on FDA's Centers to adequately regulate these industries coincides with an unprecedented amount of pressure on the agency to do much more with what amounts to much less resources in many important areas of its function. Although, as you have heard, all of FDA's Centers have an interaction with the biotechnology industry, I will limit my comments to some of the threats which exist in CBER (biologics) and CDER (drugs).

Issues which transcend any particular part of the FDA include the adequacy of the intramural and extramural research base for informing the regulatory process and, related to this but not limited to research, the atmosphere in which those who are involved in the review process are working and are (or are not) able to have their scientific, evidence-based decisions prevail as a basis for regulation.

Center for Biological Evaluation and Research

The clearest way of illustrating the dangers of inadequate funding of the government research necessary for safe and effective regulation of biologics is with a recent example. As a consultant to FDA's Vaccine Advisory Committee, I was asked to participate in a recent meeting prompted by the submission to CBER of several applications to do human studies on vaccines produced from animal or human tumor cell lines. For more than four decades, the use of such tumor cells to produce human vaccines has been off-limits and, without discussing the specific vaccines at the open session of this meeting, the safety problems which could arise were discussed. At this meeting, held on November 19, 1998, we heard an excellent series of presentations by CBER researchers, outlining the kind of research CBER itself would have to do in order to establish the kinds of tests and precautions that were necessary in order to be able to safely proceed with these new sources of vaccines. An extremely important point made by one of the CBER researchers, Dr. Philip Krause, was that this kind of research had to be a "public" function because it was not the kind of research that the industry could be reliably expected to do

on its own, given its own self-interest.

We were asked to "comment on CBER's approach to evaluate neoplastic [cancer] cell lines that are proposed for use in vaccine manufacturing." There was near-unanimity among our advisory group that the carefully-planned series of tests and research by CBER would be extremely essential in assuring that the subsequent requirements for testing and possible approval of these vaccines would result in safe and effective vaccines. But there was also concern, expressed by most members of the advisory committee, that, given the recent severe cuts in CBER research funding, the resources necessary to accomplish this critical research might not be available. Thus, we recommended that our approval of the CBER research plans was contingent on the assurance that the resources needed to do this research had to be made available.

There are several important functions of CBER research: to facilitate the approval of safe and effective products; to support decisions to withdraw products found to be unsafe; and to support informed decision-making in the prevention of and response to public health crises. All of these functions are threatened by cutbacks in funds and the number of people devoted to research.

From various sources, I have gathered data which demonstrate some of the recent cut-backs in funding and resources for CBER. From FY 1995 through FY 1998, the number of FTE's (full-time equivalent positions) devoted to research decreased from 206 positions to 146, a drop of 29%. In contrast, the FTE's allocated to the pre-market review of applications stayed almost exactly the same, going from 340 in FY 1995 to 346 in FY 1998. Thus, the PDUFA-funded support for review of applications has been maintained while the funds and positions for research have been severely cut. (Aside from salaries to support research positions, operating funds for non-salary functions in CBER have also taken a major hit. From FY 1994 when the overall CBER operating budget was $41.5 million, there has been a decrease to $32.1 million in FY 1998, a cut of 23%. Operating funds for research had the biggest loss.

Center for Drug Evaluation and Research

It is with respect to the products regulated by CDER that the Health Research Group has spent the largest portion of our time. I would like to discuss two topics. First, important intramural and extramural CDER research functions, both of which have been drastically reduced in the past few years just as the number of tasks demanding such research has significantly increased. Second, I will briefly discuss the results of a recent study we conducted of CDER NDA (new drug application) reviewing medical officers and the implications of these findings for the integrity of the drug approval process.

CDER research can do many things, but a primary component, in addition to adequate epidemiologic surveillance over the greatly increased number of new drugs approved by CDER in the past several years, should be to support policies that are now expressed in the many guidances that the Center is publishing. These guidances/policies cover the following areas,

among others: 1) pharmacology/toxicology (nonclinical studies); 2/ early-phase exploratory studies; 3/ late-phase confirmatory clinical studies; and 4/ post-marketing studies and reports.

The kind of research that CDER can do can be of great benefit not only to the public but also to regulated industry by supporting the best (most efficient, most cost-effective) tests to address questions about safety, efficacy, dose, and product quality.

A clear example of the need for such research relates to the recent FDA pediatric initiative concerning the special needs for studies in children for drugs which are going to be used in this age group. Pharmacologic studies of how to best test the distribution, metabolism and action of drugs on various organs in children are needed to conform to the recent pediatric initiatives. None are currently being supported by the FDA. Like the aforementioned need for studies to learn how to best test vaccines made from new sources, this needs to be a public, not a private function. Other inadequately-funded FDA/CDER research functions include how to search adverse event reporting databases to optimize signal generation of previously undetected or under-detected adverse drug reactions and better ways to develop safety/efficacy information..

CDER has an exciting program which offers a research experience for a small number of drug reviewers to provide professional development for them and to support the review process when specific questions arise. Both aspects are critical to a high quality, efficient review. This program, funded at only $100,000 to $200,000 a year for all of CDER (with a total of almost 200 reviewing and supervisory medical officers) is only a drop in the bucket of what could be done to enhance the scientific underpinnings of the review process by providing more research exposure for reviewers.

Despite the increased need for a variety of epidemiologic/surveillance and pharmacologic research, the budget for such activities, both within CDER and for the extramural research which it funds has decreased dramatically and dangerously. For example, between FY 1994 and FY 1998, the number of FTE's in CDER's Office of Research and Testing decreased from about 138 to about 79, a decrease of 43% in personnel. With their salaries and benefits estimated at an average of $90,000 per FTE (a decrease of $5.3 million) and operating budget (non-salary expenses) decreases from $2.8 million in FY 1994 to about $750,000 in FY 1998, the overall decrease in the budget for this important part of CDER was more than $7.3 million from FY 1994 to FY 1998, an overall decrease of well over 50%.

The extramural FDA program, which funded important pharmacologic research at centers of excellence such as Georgetown, Johns Hopkins, the Uniformed Services Medical Schools, and other academic institutions has also been drastically cut in recent years. In FY 1995, the spending was $11.6 million but, by FY 1998, it had decreased to $3.2 million, a cut of 72%. The research funded by these extramural programs included:

- Identifying the life-threatening interaction between the antihistamine terfenadine (Seldane) and erythromycin.

- Establishing a lower, potentially less-sedating dose of the antihistamine, chlorpheniramine.

- Examining gender differences in the rate of a life-threatening cardiac arrhythmia associated with the drug quinidine.

- Conducting studies of drug bioequivalence (suitability for substitution) for widely-prescribed drugs such as digoxin and phenytoin.

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Survey of CDER Reviewing Medical Officers

In September 1998, we mailed a seven-page questionnaire to reviewing FDA Medical Officers. All Medical Officers were guaranteed anonymity. Reminder mailings were sent to all Medical Officers in September and October 1998.

- Fifty-three out of 172 Medical Officers responded (31%).

- Nineteen Medical Officers identified a total of 27 new drugs in the past three years that they reviewed that they thought should not have been approved but were approved.

- Five Medical Officers identified a total of six new drugs that they reviewed in the past three years that they thought should have been approved but were not approved.

- Asked how they would compare the current standards of FDA review for safety and efficacy to those in existence prior to 1995, 17 Medical Officers described the current standards as "lower" or "much lower," 13 described them as "about the same" and six described them as "higher." None described the standards as "much higher."

- One Medical Officer stated: "My feeling after more than 20 years at FDA is that unless drugs cannot be shown to 'kill patients' outright then they will be approved with revised labeling and box warning."

- Twelve Medical Officers identified 25 new drugs that they reviewed in the past three years that in their opinion had been approved too fast.

- Thirty-four Medical Officers stated that the pressure on them to approve new drugs was "somewhat greater" or "much greater" compared to the period prior to 1995.

- Nineteen Medical Officers stated that the pressure on them to approve a greater proportion of new drugs was "somewhat greater" or "much greater" compared to the period prior to 1995.

- One Medical Officer stated: "We are in the midst now to approve everything but to describe drug weaknesses in the label. As one high ranking official said 'Everything is approvable. We can use the labeling creatively to lower the problems.'"

- Seventeen Medical Officers identified a total of 28 new drugs for which they were the primary reviewer in the past three years that had only been approved because post-marketing studies were required.

- Eleven Medical Officers stated that, compared to the period prior to 1995, the frequency of drugs being approved that would not have been approved without requiring post-marketing studies was "somewhat more common" or "much more common." Twenty Medical Officers said that this frequency was "about the same."

- Nine Medical Officers identified 19 new drugs that they had reviewed in the past three years that had been inappropriately shifted to the accelerated approval track.

- Thirty-six Medical Officers reported that they "somewhat disapprove" or "strongly disapprove" of permitting drugs to receive accelerated approval solely on the basis of having a unique mechanism of action. Seven Medical Officers stated that they "somewhat approve" of this practice.

- Nine Medical Officers reported a total of 23 inappropriate phone calls in the past three years regarding a drug they were reviewing, usually from the sponsor.

- Eight Medical Officers reported 14 instances in the past three years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved.

- Thirteen Medical Officers identified 18 occasions in the past three years when a supervisor, usually their Division Director, had asked the Medical Officer to change his or her opinion to agree with the supervisor's, usually in a direction favoring approval.

- One Medical Officer reported: "In the last 2 years, I recommended that two drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards."

In summary, our report documents a worrisome and dangerous pattern at the FDA whereby increasing pressure on medical officers from Congress, the industry and within the agency has led to a large number of inappropriate drug approvals and declining drug approval standards.

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Conclusions

Although there have been many studies, reports and statements confirming the importance of a strong research base to FDA's activities and recommending structural changes in FDA research which would facilitate this, when push has come to shove, the White House, OMB and, as far as can be determined, HHS, have not forcefully or successfully advocated for adequate funds to be devoted to these research functions. Nor have FDA leaders been allowed to forcefully and publicly make the case concerning the predictable adverse public health consequences of the current deteriorating status of FDA research funding. Instead, efforts to allow the use of portions of the PDUFA (user fee) funds to go for FDA research in the recent reauthorization of this law in 1997 were strongly and successfully opposed by most if not all of the drug and biotech industries and their trade associations. Instead of resisting legislative attacks and other industry/congressional efforts to otherwise endanger the drug, biologics and other FDA approval processes, the leaders in the executive branch have boasted about "re-inventing government," ignoring the growing threats to the health and safety of Americans who use these regulated products.

There is no reason why the important research functions of the FDA should not be entirely funded through the budgetary/appropriations process. The need for such funding is too critical to be left to the pressure of industries which do not want their PDUFA dollars going to support FDA research. The current NIH budget appropriation was approximately $15.7 billion for FY 1999. An amount at least equal to or greater than 2% of this amount (not to be subtracted from the NIH budget) should be allocated to fund FDA research functions each year. This would amount to approximately $314 million in FY99, well in excess of the current amount allocated to all of FDA research.

The history of public health-improving changes in FDA authority is littered with examples of tragedies, preceding the positive changes, which occurred because the FDA did not have the authority or resources to adequately police industry and avert these product-caused deaths and injuries. Only then were laws such as the 1938 and 1962 drug amendments and the 1976 and 1990 medical device amendments enacted. It is unacceptable to wait for more such preventable deaths and injuries before remedying the current research and regulatory problems at the agency. It can only be hoped that the next changes in regulatory authority and funding for the FDA will once again be in a positive direction, reversing the dangerous, negative twists of the past several years. If not, we are all at risk.