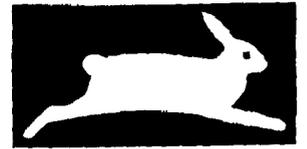


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**FDA Report on Science and Technology
"FDA Science and Mission at Risk"**

People for the Ethical Treatment of Animals (PETA) is the world's largest animal rights organization, with more than 1.8 million members and supporters who care deeply about the plight of animals in laboratories. An important first step was made in December of 2006 when Commissioner von Eschenbach requested that the Science Board form a Subcommittee to assess whether the science and technology infrastructure at FDA can support its current and future regulatory demands. The following comments are in response to the Subcommittee's findings, titled *FDA Science and Mission at Risk*. While the conclusions of the Subcommittee found that FDA suffers from enormous scientific deficiencies and is not able to handle its current demands, the report emphasizes solutions. PETA would like to weigh in similarly so that FDA can implement changes to prevent further degradation and crisis.

FDA's responsibilities have dramatically increased in the last four decades and have transformed FDA from an agency that was primarily used as law enforcement (in the 1970s) for tampering and misbranding issues to an agency expected to regulate using cutting-edge science. This change has left the Agency trying, but failing, to catch up with its growing responsibilities. As the Subcommittee states, "effective regulation requires that the scientific competency within FDA matches or exceeds an applicant's knowledge." We agree with the Subcommittee's findings in that the Agency does not have the capacity for the increased scientific breadth and specialization it requires to manage all areas of FDA's responsibility competently.

Demands on FDA have been amplified in recent decades due to scientific advances, increased product complexity, the emergence of challenging regulatory problems, and globalization. Therefore, it is not surprising that FDA, without adequate incremental updating and funding increases, has been left without recourse and the Subcommittee findings illustrate that ill-trained, and inadequately educated staff make not only delayed decisions, but they often make incorrect decisions. This, simply put, is a threat to public health. FDA structure and staff need a major overhaul and those that remain in FDA's employ should be staff members with up-to-date scientific training and the specialization necessary to regulate new products effectively.

While attending regulatory meetings in Europe and scientific meetings that include European regulators, it is clear that FDA's reign as a capable, world leader is no longer recognized. When FDA is brought up in the context of international regulatory standards the concept is met with overt cynicism. The reason for the lack of respect for FDA internationally is precisely due to FDA's steadfast use of outdated assays that are ineffective for ensuring the safety of products intended for humans.

The recently published National Research Council report entitled *Toxicity Testing in the Twenty-First Century: A Vision and a Strategy* reports that "Toxicity testing is approaching a scientific pivot point...It is poised to take advantage of the revolutions in biology and biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin." Based on this view given by respected toxicologists, we hope to see considerable changes made at FDA so this vision can be realized in the short-term.

The Subcommittee's Major Findings

Finding 1.2:

The Subcommittee finds that, "[T]he FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak." This is a sweeping statement that sums up many of FDA's specific inadequacies. We find that FDA is not yet capable of analysis using up-to-date analytical methods, cell-based assays, and human-based 'omics' studies. These are advances of the last decade or more and have proven to be predictive and relevant to human risk management.

FDA has long been thought of as one of the world's premier regulatory agencies but at this point FDA's role as world leader is in question. The Subcommittee states, "not only can the Agency not lead, it cannot even keep up with the advances in science." Reactive, "fire-fighting regulatory posture" is not adequate for a technologically advanced nation with risks coming from global markets. FDA should be setting precedent rather than requiring animal experiments of the past, which have proven to be a waste of money and lives. In agreement with the current findings, systems biology (omics studies) should be utilized to their fullest potential. Science is capturing cellular reactions to drugs and chemicals and these valuable tools should be used and accepted by FDA. The best way to measure human cellular reaction is by using/measuring human cells reacting in a relevant manner.

Figure 1 of the report, *Food and Drug Administration-Regulatory Industry (FY2006)*:

With 800 new biologics on the market in one year and the responsibility for reviewing \$40 billion in investments during 2006, it is striking that FDA's Center for Biologics Evaluation and Research (CBER) refuses to accept potency or efficacy data using the most up-to-date methods, in most cases. Instead, preference has been given to experiments like the NIH rabies batch potency method for vaccines which has a 400% rate of variability from test to test. Inexplicably, FDA has dug in its heels and delayed implementation of the ELISA method which is used with great success in the European Union (EU). This example can be extrapolated to the majority of vaccine batch potency and efficacy testing. The methods by which FDA deems vaccines safe and effective can do neither. These old-fashioned methods contribute to public health risk, decreased accuracy, and increased cost.

At the Center for Drug Evaluation and Research (CDER), the picture is bleak. CDER regulated \$275 billion in pharmaceutical sales from 2,500 U.S. manufacturers and 2,500 foreign manufacturers, and approved 12,000 new drug products in 2006 by staff who do not have proper, modern scientific training causing the outlook for public safety to be more grim. At best, each of these new drugs has, by FDA's own figures, an 8% chance of receiving FDA New Drug Application approval when moving from preclinical studies (including animal experiments) to clinical trials (human studies). Even after approval and marketing, about half of drugs are either relabeled or withdrawn for serious adverse effects not predicted during animal testing. While drug development methods change with the times, so too should the testing methods and CDER's methods of evaluation. The disparity between the science used in the labs to develop new compounds and the methods that are required by FDA to deem them "safe" is discouraging and alarming. While state-of-the-art methods are employed in R&D labs, these methods are not carried over to safety testing where the most precise methods are needed. Instead, after development in the most sterile, modern laboratories, the substances are then injected, inhaled, and ingested by animals in their last terror-filled hours of life. Not only are these test results meaningless, the means of gathering reams of irrelevant data is gathered on the backs of millions of animals who share little of our complex biology.

The Center for Devices and Radiological Health (CDRH) regulates industry sales upwards of \$110 billion yet cannot seem to publish a compendium of biocompatible materials that would reduce redundant animal tests considerably. We have written to Dr. Daniel G. Schultz regarding this important issue but have not received a response. Despite working alongside an industry expert with decades of device policy experience who is able to

recognize areas of inexplicable redundancy and waste, we cannot seem to get CDRH to act on its own 1997 commitment to publish this complete compendium of biocompatible components. Is this Center so broken that even the most basic step in streamlining is impossible?

The Office of Regulatory Affairs (ORA) regulates more than 123,000 business establishments from coast to coast and in Puerto Rico. When calling the ORA headquarters this year, no one to whom we spoke was capable of explaining how similar establishments owned by U.S. companies would be regulated in China and similar developing nations without their own animal welfare standards and with differing capacities of GLP. Because companies based in the U.S. but with laboratories/contract laboratories in developing countries are allowed to operate and import without oversight, citizens are now at greater risk due to the substandard facilities in these countries that are operating without inspection. A recent report by the *Washington Post* also states that at its current pace, FDA would "need at least 27 years to inspect every foreign medical device plant that exports products to the United States, 13 years to check every foreign drug plant and 1,900 years to examine every foreign food plant, according to government investigators"

(http://www.nytimes.com/2008/01/29/washington/29fda.html?_r=1&oref=slogin). All of this just to inspect each facility one time, let alone keep up with its current operating practices. This level of disarray and self-regulation by manufacturers is no less dangerous than not having a regulatory agency at all.

FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for ensuring the safety of \$417 billion worth of domestic food, \$49 billion in imported foods, \$60 billion in imported cosmetics, and \$18 billion in dietary supplements; the Subcommittee finds that this Center in particular is in a state of crisis. Findings show that this major crisis is due to FDA's inability to keep up with medical advances that would allow it to accomplish its task of ensuring food safety much more reliably and efficiently.

The subcommittee finds that FDA does not have the capacity to ensure the safety of the nation's food supply and recommends that CFSAN's and CVM's scientific base be rebuilt so that they become capable of inspecting and enforcing regulations commensurate with their regulatory responsibilities. An example of CFSAN's lack of scientific rigor is the lax and illogical regulations surrounding shellfish toxin testing. Not only has CFSAN not yet implemented the Lawrence Method of HPLC (AOAC validated more than a year ago), but it has opted to use the lowest common denominator to attempt to regulate shellfish/detect shellfish toxins. The mouse bioassay (MBA) is of specific concern not only because it is a brutal and inaccurate test, but also because, data are not reproducible from mouse to mouse or from lab to lab.

Mice have been found to be very sensitive to toxins to which humans have never had adverse reactions and vice versa. Analytical methods are available for each class of toxins and were used in Germany (from the mid-1980s until it joined the EU) with a clean record for public health protection. The MBA is not capable of giving experimenters information regarding which toxin has caused the mouse to convulse and die. Instead, the mouse dies a painfully drawn-out death and the experimenter simply records the time it takes the mouse to die and applies an inaccurate formula that is not capable of calculating the precise concentration of toxins found. In contrast, analytical methods available at this time are capable of delivering a precise toxin concentration profile. Other countries are already leading the way showing the world that analytical methods are far superior. We hope to see this simple example of CFSAN's shortcomings changed in the very near future.

Figure 3: Food And Drug Administration Regulatory Activity (FY2006):

Due to FDA's short-staffing crisis and the "major gaps of scientific expertise in key areas" FDA strategy seems to have shifted to one that encourages and/or requires the submission of an extreme number of old-fashioned, yet familiar assays to FDA. This allows FDA staff to judge each of the new PMAs, BLAs, INDs, 510(k)s, HDEs, IDEs, etc., with the same old familiar assays despite the fact that they are neither predictive or reproducible. Because FDA's staff is unfamiliar with current, cutting-edge and reliable tests, millions of dollars, incalculable amounts of time, and untold numbers of animal lives have been wasted. All of these problems are due to a simple, yet catastrophic inability to stay up-to-date.

We implore the FDA to make immediate changes in the requirements it has of its staff. It is the FDA's main task to remain abreast of the most capable and high-throughput test methods. FDA should reevaluate the employment of staff members charged with reviewing submissions for new products to insure that they are of the highest caliber and have stayed current with new advances. Much of what FDA's staff does is based on their current knowledge as well as on common sense. Emphasis on both of these traits is important so that test plans with the most efficient strategies using accurate methods are accepted by FDA and superfluous experiments are no longer required.

Finding 2.3 The Changing Nature of Science:

A 2004 program entitled *The Critical Path Initiative* mapped out a plan that was intended to transform the FDA into an agency with 21st century science-based standards. The recent, FDA-requested recommendations made by the Institute of Medicine (IOM) called for the application of new scientific and bioinformatics tools and suggested extensive external collaborations to gain access to expertise and databases lacking at FDA. The launch of the CPI in

2004 and the lack of changes seen at the FDA has left "the public understandably confused by the growing disconnect between the promises of cutting-edge science and the reality of clinical benefit." We echo the Subcommittee's recommendation that FDA hire leading scientists in cutting-edge specialties so that modernization and streamlining can be realized at FDA. Finding 3.1.2 reiterates FDA's inability to regulate new products with new science. We agree that FDA must provide a standardized approach to assessing new science with newer methods of analysis.

We wholeheartedly agree with IOM's analysis and recommendations related to FDA's need to implement new statistical methods to evaluate data, new methods to interpret microarray data and systems biology experiments. We agree that the FDA needs to upgrade its abilities in statistics and biomathematics so that high-throughput data do not go to waste.

Many groups have charged FDA with shirking its responsibilities when it comes to nanomaterials in cosmetics, pharmaceuticals, and devices. Not only do we agree with this assertion, but it is also clear that FDA cannot successfully begin regulating nanomaterials when it has not confidently designed a plan to test traditional materials. We hope that FDA has received and read our previous comments regarding nanomaterial toxicity testing (2006N-0107) and nanocosmetics, specifically (197N-0038). As an expert nanomaterials policy advisor, I trust that FDA will find these recommendations useful.

Section 3.1 Science Capability, Capacity, and Organization:

The Subcommittee finds that FDA's substandard programs for judging scientific staff performance, allowing for professional development, and taking advantage of external collaborations all contribute to its major staffing problems. Inter-Center collaboration along with establishing methods for professional development and metrics to gauge individual development should be implemented so that incompetent staff are not retained and paid with tax-payer dollars.

Section 4: Overarching Findings of this FDA Review:

In addition to the major findings discussed above, it was noted that even when FDA seeks outside opinion, "excellent FDA reviews are seldom followed." Asking for help without implementing any of the suggestions is another waste of time and taxpayer money. FDA is charged with keeping our food and drug supply safe, and in order to exact change and to be capable of FDA's mission major changes are acutely needed, and an overhaul of the outdated structure at FDA is required. Because FDA cannot be expected to achieve the goals of its mission without proper funding, we fully support increases in FDA funding to be put towards modernization, staff training,

implementation of Subcommittee recommendations, and the many areas that animal experiments can and should be replaced.

We look forward to seeing FDA's transformation and are happy to offer our expertise. Please do not hesitate to contact me by phone 757-622-7382 ext. 8119 or via email at SamanthaD@peta.org on this urgent matter.

Sincerely,



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