nature biotechnology
VOLUME 14 APRIL 1996

FDA drug approvals: No worse is simply not good enough

The US Food and Drug Administration (FDA, Rockville, MD) was recently put on notice by the US Congress. At the end of last year, Republican Senator Nancy Kassebaum of Kansas introduced the FDA Performance and Accountability Act as a kid-gloved way of bringing the FDA in line with the so-called "Contract with America." The new thinking in Washington these days is that government agencies should be facilitators of business rather than stunters of its growth. According to this thinking, the FDA, as public servant, should be held accountable for the extra burden it puts on the public when it causes unjustifiable delays in drug development, in much the same way that drug developers are forced to justify their therapeutics' safety and efficacy to the FDA.

Special interest groups, such as the Biotechnology Industry Organization (BIO, Washington, DC) and the Pharmaceutical Research and Manufacturers of America (PhRMA, Washington, DC), as well as patient activist groups, have applauded the Kassebaum effort as long overdue. "The United States leads the world in drug discovery," says Gerald J. Mossinghoff, PhRMA's president, "now it's time for it to lead the world in drug approvals." "There are people waiting for new medicines being developed by biotechnology companies," says Carl B. Feldbaum, BIO's president, "The single goal of the reform effort should be to get those medicines to the people who need them as soon as possible."

FDA Commissioner David Kessler recently responded to these criticisms—and to the call for reform—at the Massachusetts Biotechnology Council annual meeting (Boston, MA): "It is time to put to rest the incorrect perception that American patients generally suffer because of a so-called drug lag," he said, "While there will always be an occasional exception, we approve most important new drugs first."

Is there a drug approval lag or not? "In many ways, the US is comparable to the UK," says Stuart R. Walker, director of the Centre for Medicines Research (CMR, Carshalton, UK), and one of the authors of the preliminary report (part of which will be published this month in CMR's newsletter) from which Kessler took some of the data to justify his remarks. While the report stresses that there are limitations as to the kinds of conclusions that can be drawn from comparisons between mean or median approval times, as a rule of thumb, Walker says, "Between 1990 and 1995, review times in the US were no worse than anywhere else." The report states that, for drugs submitted within six months of each other in the US and UK, the US reviewed six of nineteen compounds in virtually the same time as the UK, while lagging behind in nine reviews. Of the nine reviews in which the US came in second, the greatest difference between US and UK approval times was greater than a year in only two cases. The report goes on to show that the FDA has made steady improvement in lowering its mean approval times since the late 1980s—most dramatically in 1994 (the latest year for which final figures are available).

Does this mean that the Congress, drug developers, and patient advocacy groups should drop their efforts to reform the FDA? Absolutely not. While we applaud the FDA's apparently successful efforts to streamline the agency, and hope that the agency will continue to improve, the fact that it is "no worse than anywhere else," is not sufficient grounds to recommend that it continue to be run without independent oversight. The agency needs to be accountable for its actions, and despite Kessler's efforts to show that it will improve on its own, there is little doubt that these improvements would not have occurred without the sustained lobbying of drug makers and patient advocacy groups alike.

The real question for biotechnology drug makers is whether the measures proposed by Kassebaum will be sufficient to propel the FDA into the 21st century. As pointed out in Stanley T. Crooke's article "Comprehensive Reform of the Drug Regulatory Process" (*Bio/Technology* 13:25, January 1995), methods of drug discovery and development have undergone a revolution—which the FDA has failed to match. While simple FDA reform may aid traditional pharmaceutical development, will it really help reduce the regulatory burden on the innovative therapeutics that will continue to emerge from biotechnology? What the CMR report and Commissioner Kessler fail to point out in their analysis is the fact that for emerging biotechnology companies, being forced to wait 9 out of 19 times for periods of more than a year for US approval versus UK approval is not trivial. For biotechnology companies, and for patients waiting for these therapies, such delays can be devastating.

One alternative to the Kassebaum legislation, a recent proposal by the Progress and Freedom Foundation (PFF, Washington, DC), suggests it is time for the FDA to undergo a dramatic reformatting—rather than simple reform—to catch up with the technologies it is regulating. The authors of "Advancing Medical Innovation" suggest that it is only, "through a fundamental change in the framework used to bring new medical products to market. . .." that total development times and product availability times will be improved. The authors propose to have oversight of clinical product development and reviews of the results performed by the private sector. The FDA's function would be to license and oversee private sector "drug certification bodies" (DCBs), which would consist of the "experts qualified by scientific training and experience" that the law currently requires to ensure the regulatory compliance of all parties in the system, and to have final review and signoff of any recommendation the DCBs make for approval. The FDA would also manage the national drug safety system, as it does now. The proposal concludes that removing the inefficiencies of a monopolistic federal agency from these steps and establishing private sector competitors would enable better service to be offered to sponsors while maintaining standards of safety more similar to those now employed in Europe.

So far, the PFF proposal has received little attention because it has been overshadowed by the proposed Kassebaum legislation. But the idea of reformatting the FDA—not just reforming it—should be given serious consideration by all legislators and drug makers and patients who are not satisfied with an FDA that is "no worse than anywhere else."

Xenotransplantation and the "yuk" factor

When the Nuffield Council on Bioethics (London) issued its recent report—"Animal-to-Human Transplants: The Ethics of Xenotransplantation"—it was probably inevitable, regardless of the content of the report, that the general media would seek out the flaws in

the technology. But when the report itself highlighted the transmission of disease from animals to humans as one of the council's major concerns, the probability became certainty. Much of the newspaper, television, and radio coverage of the Nuffield Council report has focused strongly on the need to avoid cross-species infection.

Replacing human tissue with animal cells and organs clearly raises issues that some people will find threatening. Spare-parts surgery, using organs or cells from animals, challenges our notions of humanness, our sense of distinctness from other species. It is easy to find sympathy for those who are repelled by xenotransplantation—even if that repulsion has visceral rather than cerebral roots.

In the face of the "yuk" factor, the scientific, knowledge-based position put forward by authoritative bodies must be both accurate and representative. The Nuffield Council concluded that "the risks associated with the possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical, therefore, to begin clinical trials of xenotransplantation involving human beings."

The higher risk of disease transmission to humans from primates persuaded the Nuffield Council to favor pigs over primates as sources of transplant organs. Its report points to a macaque monkey form of herpes B virus that causes a rapidly fatal encephalitis in humans. It also draws attention to the similarities between the simian and human immunodeficiency viruses (SIV, HIV): Journalists were left to draw their own conclusions about SIV and AIDS. What was lost in all of this distracting detail, however, was the even greater risk that exists of disease transmission in human-to-human transplantation.

Before recombinant DNA, the major sources of insulin for diabetics were the pancreases from pigs and cattle. Despite the fact that there were several million diabetics taking injections of animal insulin several times daily, there were very few, if any, reported cases of bovine or porcine disease transmission. Insulin, of course, was a purified compound, not a living preparation. However, vigilant readers will also recall that purified proteins extracted originally from human sources— human growth hormone extracted from the pituitary glands of human cadavers, for instance, or antihemophilic factor VIII extracted from blood—have far worse records of disease transmission than does animal insulin (see "Bad blood settlement in Japan," p.410). The simple fact is that human beings usually get their diseases from other humans.

The Nuffield Council report also raised the possibility that the animal organs themselves would be susceptible to animal disease, especially in the case of transplanted lungs. Very little is known about these risks, says the report, and it advises that would-be organ recipients should be advised of the possibility of infection. Naturally. But then perhaps what animal organ recipients should really be advised of, if they want to steer clear of infection, is to reconsider any plans they might have had for a career in pig-farming. That, one suspects, would not be an untenable burden at least for the 98 percent of us who forsook agriculture for the urban lifestyle a long while ago.

The Nuffield Council report also draws attention to the possibility that prion diseases can pass from one species to another, thereby raising the specter of spongiform encephalopathies. This is simply another distraction. No one is contemplating xenotranplantation from cattle, mink, or cats (although a patient did receive a sheep heart in 1968 and died instantly). Furthermore, as the report itself describes later, the transmission of prion diseases normally occurs by transplantation or by eating infected material. If there are pig prions, avoiding bacon and ham would seem to be as wise a course of action as curtailment of xenotransplantation.

There are, undoubtedly, some very nasty diseases that affect both animals and humans. There are also very many more diseases that are virtually species-specific and highly unlikely under any circumstance to cause any human disease, ever. Furthermore, one could call as witnesses for the defense many animal pathogens whose impact on human beings has been very beneficial. Edward Jenner's original observations on the protection against variola (smallpox)—that exposure to vaccinia (cowpox) conferred to milkmaids—spring to mind. Despite the demise of variola, vaccinia is still finding wide employment—as a recombinant expression host in vivo for a variety of disease-antigen genes in experimental live vaccine. So is fowlpox virus.

Indeed, there is a general message from vaccinologists to those who are worrying about infection in xenotransplantation. From Louis Pasteur—who produced his first rabies virus by passaging rabies through duck brain cultures—to modern producers of influenza vaccines who still cultivate attenuated viruses in chicken eggs, most experience indicates that growing viruses in the cells or tissues of other species can make the infection agent less pathogenic, less fit for its invasive, disease-causing role, and less likely, therefore, to cause a problem in humans.

Nothing here is meant to indicate that infection is not a problem in xenotransplantation. In immunosuppressed patients, it most certainly is. But to address the problem incompletely is to misrepresent the risk. And passing references to headline-grabbing diseases that are in all likelihood irrelevant—Ebola gets a mention as well as AIDS and bovine serum encephalitis—distract from the real disease issues. Asilomar and its consequences for public attitudes to recombinant DNA should alert the research community to the dangers of being too "responsible" in the face of uncertainty. If we don't know something, lets just say so and leave it at that.

Ex Novartis ad astra

The name "Novartis," for the new entity that was Ciba-Geigy and Sandoz, may be pretentious but it has merit, even hidden depth.

The first is that a new name clearly signals a clean beginning and discards the banners to which old loyalties and rivalries might have been directed.

"Novartis" also has a certain style. Not yet elegance, of course. That would be too shocking, at least for those involved in the pharmaceutical industry, who, in their naming of drugs, seem to delight so in the torture and corruption of the language. "Novartis" cannot — in a way that so many merged corporate "famous names" can—be mistaken for an advertising agency or a firm of New York lawyers. A design consultancy? Perhaps.

Novartis has classical roots. It is a reversal and diminution of the Latin "artis nova," meaning "new skill" or "innovation." The intended innovation, no doubt, is internal. But, as with other life science company mergers, there will be implications for smaller innovative companies, too. The recent creations of the lawyerly Glaxo Wellcome (London), Pharmacia and Upjohn (Kalamazoo, MI and Stockholm, Sweden) and Hoechst Marion Roussel (Frankfurt, Germany), for example, have involved substantial job losses. This means that small biotechnology companies may find themselves able to recruit unexpectedly available experienced pharmaceutical executives at prices they can afford. And more adventurous former Ciba or Sandoz employees may turn entrepreneur and seek financial backing to establish their own companies—as did former Burroughs-Wellcome executives in founding Triangle Pharmaceuticals (Research Triangle Park, NC). On the downside, partnering may get somewhat harder. In the midst of introspective postmerger consolidation, smaller companies may find it more difficult to get their pitch across to the new megafirms. And fewer, bigger life science giants means fewer players at the biotechnology buying table.