

Politics Versus Science

in Biomedical Research and Development

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Decisions to accelerate the approval of AIDS combination drugs, reject over-the-counter status for the morning-after pill, and limit support for stem cell research reflect mounting political pressures.

In May, FDA held its 10th annual Science Forum to highlight the work of agency researchers and, by reference, the scientific underpinnings of agency regulatory decisions. FDA's new Critical Path Initiative, which aims to spur more-efficient drug development (see *Pharmaceutical Technology's* May issue of Washington Report), provided a focal point for discussing staff research involving genomics, diagnostic imaging, nanotechnology, proteomics, and other cutting-edge biomedical fields.

However, little was said at this event about the growing tensions between science and politics related to biomedical research and product development. While pharmaceutical researchers in both public and private organizations prefer to believe that scientific evidence provides the basis for government regulatory and policy decisions, many initiatives related to drug development and production are increasingly shaped by and respond to political concerns.

The heightened debate regarding drug importation is a prime example. Despite a general consensus among scientists, economists, and policy experts that more-liberal drug importing from Canada and other nations raises serious public health concerns, mounting demands for access to cheaper drugs are likely to prompt congressional approval of import legislation. Similarly, the desire of policymakers to reduce spending on prescription drugs has increased support for generic medicines—a trend shaping the emerging debate regarding “follow on” biologics.

Politicians increasingly are weighing in on the need to facilitate public access to new medicines, particularly experimental treatments for cancer and other life-threatening diseases, even when the results are not scientifically strong. Several members of Congress, for example, are keeping a close watch on how FDA deals with two new experimental cancer therapies that recently were rejected by an FDA advisory committee.

Election-year politics appear to have played a role in blocking broader access to the morning-after pill, “Plan B,” as well as possible loosening of federal policies limiting stem-cell research. And

efforts to fast-track FDA approval of new combination AIDS therapies reflect a sharp policy reversal prompted by international pressures to make these low-cost treatments available to third-world nations. All of these developments promise to have significant effects on pharmaceutical manufacturers as well the broader research community.

Blocking Plan B

Probably the most publicized example of politics trumping science on the regulatory front is FDA's recent rejection of over-the-counter (OTC) status for Plan B. There was strong scientific data supporting the change, as Plan B has been available for years on a prescription basis, providing ample evidence of its safety and effectiveness. Last December, members of two FDA advisory committees voted 23 to 4 to approve the OTC application from Barr Pharmaceuticals (Pomona, NY), a recommendation that FDA staffers usually follow. In this case, agency officials responded to high-level demands to find a legitimate rationale for rejecting the application.

The rejection occurred in May when Steven Galson, acting director of the Center for Drug Evaluation and Research (CDER), sent a nonapproval letter to Barr. Generally, it is unusual for the CDER chief to sign such a letter—an indication that Galson had to overrule a proapproval decision from his staff. CDER could have issued an “approvable” letter that would have required additional data or research for Barr to market the product OTC—an option that makes full rejection more suspect.

FDA evidently based its nonapproval decision on the lack of data about the appropriate use of the therapy by young women (under 16 years old), thus alluding to the possibility that easy access to Plan B would encourage teens to engage in riskier sexual activity. FDA also justified its action on the fact that Plan B remains available by prescription and is obtained fairly easily from clinics. Barr and its supporters note that the treatment is effective only if it's used within 72 hours after unprotected sex, thereby making easy access to the product important.

In response to FDA's action, Barr is seeking dual status for Plan B in which adults with proper iden-

tification would have OTC access while patients under the age of 16 would be required to have a prescription. Such a dual-labeling system raises a host of novel legal issues that could take some time for FDA to resolve. Barr gains by avoiding additional studies about the use of the product by adolescent women, which represents a relatively small portion of the intended market.

Meanwhile, FDA's controversial non-approval decision is rekindling charges that agency regulatory policy too often stymies patient access to new treatments. More than 40 members of Congress sent a letter to Acting FDA Commissioner Lester Crawford urging a review and reversal of the Plan B rejection. Manufacturers and political observers are wondering whether FDA is becoming more risk averse in bringing new products to market, and the agency missed an opportunity with Plan B to lay such fears to rest.

Encouraging AIDS drug combinations

In some cases, accommodating political

pressure yields positive results. The worldwide clamor for low-cost fixed-dose combinations (FDCs) of antiviral drugs to treat AIDS patients in third-world nations prompted the Bush administration to devise a fast-track approval process of these treatments that reflects FDA legal requirements and ensures product quality.

In April, Randall Tobias, US global AIDS coordinator (and former Eli Lilly chairman), explained to a Senate committee that US policy allows the State Department to purchase only those drugs for which safety and effectiveness can be demonstrated to a "stringent regulatory authority" such as FDA. He objected to the World Health Organization (WHO) program to "prequalify" certain FDCs because it would use taxpayer dollars to purchase drugs not approved for use in patients' homes. The proposal would open the door to charges that the President's Emergency Plan for AIDS Relief was foisting lower quality treatments on poor nations. US authorities said that they could not obtain manufacturer data under the

WHO program, which calls for only limited inspection of plants manufacturing generic FDCs. Tobias insisted that the United States has nothing against low-cost therapies, but it doesn't want to purchase ineffective or unsafe products that could exacerbate drug resistance.

International health agencies and AIDS organizations objected to this proposition, saying that the United States was delaying efforts to ramp up AIDS treatment efforts around the world. US refusal to purchase these low-cost, easy-to-use drugs would be costly, because public health organizations would have to spend more money for FDA-approved medicines; the policy also would create serious logistical problems because clinics would have to separate drugs purchased with US funds from other drugs. The issue came to a head in April when the William J. Clinton Presidential Foundation joined with the World Bank, UNICEF, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria to expand purchases of low-cost generic FDCs.

In response, the Bush administration

Criteria for combination AIDS drug development and approval

FDA says it will require little additional testing by manufacturers of copackaged products that combine two or three approved drugs in new blister packaging. Drug-drug interaction studies may be needed if they are not already available. Product stability in the actual dispensing packages and bulk storage and shipping containers also may need to be evaluated in addition to existing accelerated and long-term stability data. Some added testing of moisture uptake may be necessary when high-density polyethylene bottles are used in place of blister containers. FDA notes that manufacturers of copackaged products ideally would use components with identical dosing frequency and similar food instructions; if products have different dosing schedules, the packaging must clearly explain the appropriate use of each component.

For new fixed-dose combination products, testing and approval will be more complex and take longer. Although manufacturers generally will not have to

conduct additional in vitro tests or clinical studies, some bioavailability and bioequivalence data may be needed to demonstrate that an FDC product has the same rate of absorption as do the individual ingredients. In addition to all the issues involved in copackaging different products, manufacturers formulating FDCs may have to provide data supporting

- the lack of interaction between active ingredients
- adherence to quality standards for each active ingredient and the dosage form
- dissolution tests that show reproducible drug release and that the presence of two or more active ingredients does not affect dissolution performance
- stability of the combination drug product in the actual dispensing package
- excipient safety
- that manufacturing processes for each drug substance, drug product, and package meet good manufacturing practices.

mapped out a procedure for expediting FDA approval of AIDS drug combinations, which HHS Secretary Tommy Thompson announced in May at the

opening of the WHO annual meeting in Geneva. The program promises very fast (within weeks) approval of already marketed AIDS drugs that manufacturers

repackaged into easy-to-use blister packs designed to simplify dosing. FDA also will assist manufacturers in developing new combination therapies that reformulate already-approved drugs into single pills—a process that the agency acknowledged would take longer.

To encourage manufacturers to submit applications for these products, FDA issued a draft guidance 14 May 2004 detailing what sponsors have to do to gain speedy approval of combination and copackaged AIDS therapies already approved for individual therapy (see www.fda.gov/cder/guidance/index.htm). The draft guidance notes that FDA has systems in place to handle priority review and fast-track designation of critical therapies, as well as the authority to refer to existing clinical safety, efficacy data, and published reports to approve new combination drugs without requiring extensive additional testing. FDA also expects to waive user fee payments and pediatric study requirements to speed these medicines to market.

The draft guidance lists drug regimens

and components that FDA believes have sufficient clinical safety and efficacy data to support concomitant use and fit agency criteria for two- and three-drug regimens that would not need new clinical studies to gain approval (see sidebar, "Criteria for combination AIDS drug development and approval"). Manufacturers will need to propose a system for collecting and reporting adverse drug reactions in developing coun-

tries, which is an activity that governmental or public health agencies that distribute the products are likely to handle.

The policy to provide approved combination products for use in third-world nations permits generic drug makers to include patented treatments in new FDCs or copackaged products without permission of the innovator firms. In such cases, FDA could grant tentative or conditional ap-

proval to the combination drug. This approval would allow the State Department to purchase these products for use in foreign markets where the manufacturer does not enforce its patents, but not for use in the United States. FDA often issues tentative approvals for generic drugs to delay US marketing until patent expiration.

Although some skeptics complained that the FDA fast-track approval policy merely repeats what WHO already has done and thus will delay access to needed therapies, most observers applauded the initiative. Moreover, the new policy seems to be generating responses from manufacturers. Right after Thompson's announcement, Gilead Sciences (Foster City, CA) announced that FDA was granting priority review to its previously filed application for a fixed-dose coformulation of two approved antiviral medications: Viread (tenofovir) and Emtriva (emtricitabine). Both products have been on the market for more than a year, and should receive an approval decision this fall or even sooner under the new policy.

Similarly, GlaxoSmithKline is hoping for speedy FDA approval for a combination of its Epivir (lamivudine) and Ziagen (abacavir) products. GlaxoSmithKline also may develop a broader FDC with Boehringer Ingelheim's Viramune (nevirapine) product, while Gilead is working on an FDC with Merck and Bristol-Myers Squibb. These manufacturers first may develop copackaged versions of these combination drugs while testing and seeking FDA approval of new combination treatments.

Ignoring science on stem cells

While Washington policymakers responded to political pressures in regard to AIDS drugs, the Bush administration continues to maintain restrictions on embryonic stem cell research. The situation is prompting other governments and private organizations to fill the void, but the strict limits on federal support have curbed investment and have stymied progress in this area.

In August 2001, President Bush limited federal funding of embryonic stem cell research to cell lines created on or before that date. Unfortunately, less than 20 of the 78 originally identified lines now appear to be available for research. Moreover, the National Institutes of Health (NIH) is spend-

ing only \$20 million on stem cell research, despite its \$27-billion annual budget. US researchers consequently may lose their prominence in this important area, as seen in surveys indicating that more new embryonic stem cell lines are being created outside the United States and foreign researchers have access to more cell lines than do scientists in the United States. In May, British researchers opened a national

stem cell bank in the United Kingdom to store and distribute embryonic and adult stem cells to scientists around the world. The bank started with only two stem cell lines and unclear licensing policies but hopes to grow and become a main factor in setting policies for this field.

To fill the domestic funding void, states and private organizations in the United States are launching stem cell research ini-

tiatives. In May, the governor of New Jersey signed legislation to establish a \$50-million stem cell research institute. Californians seek to put a similar proposal on the November ballot. Several universities, including Harvard, Stanford, the University of Wisconsin–Madison, the University of Minnesota, and the University of California–San Francisco, are starting privately funded programs to support research on newer stem cell lines. The Harvard Stem Cell Institute, for example, aims to raise \$100 million to support dozens of researchers and specialists from hospitals and academic institutions in Boston.

The current limitation of stem cell research is emerging as a hot political issue. In April, 206 members of the House of Representatives sent a letter to President Bush urging reconsideration of the current policy, and about 50 senators have signed a similar plea for flexibility. Former First Lady Nancy Reagan made headlines a few weeks ago by strongly supporting stem cell research as a way to find cures and treatments for Alzheimer's and other diseases.

Although President Bush indicated that he would not change his limited-funding policy, NIH Director Elias Zerhouni responded to the House letter with a carefully crafted statement that offered some hope of future change to research advocates. Zerhouni acknowledged that access to additional stem cell lines could speed scientific research while reiterating the administration's policy that public funds should not encourage destruction of human embryos that have potential for life. Zerhouni subsequently explained that the current policy is based on the President's moral and ethical concerns and admittedly not on scientific evidence. The hope is that the White House might open the door for researchers to use embryos that were abandoned in fertility clinics and slated for destruction.

Although the first embryonic stem cell was isolated in a US laboratory, future advances may occur elsewhere. Carl Feldbaum, soon-to-retire president of the Biotechnology Industry Organization, said in a recent interview that he expects a demonstrable advance in stem cell research to take place outside the United States, and that the number of stem-cell lines available for research will "increase geometrically." **PT**