The Safety Risks of Innovation

The FDA's Expedited Drug Development Pathway

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"Driving Biomedical Innovation" is one of the signature initiatives of the Obama Administration and of US Food and Drug Administration (FDA) Commissioner Margaret A. Hamburg's tenure at the agency.[1] This initiative embodies administration policies that government should encourage growth and innovation rather than being the stifling blanket of bureaucracy and delay so often cited by critics of government regulation. Prominent in the agency-wide initiative is the FDA's program for speeding approval of seemingly promising new drugs, known officially as the "Expedited Drug Development Pathway."[1]

Although enabling new drugs with a favorable benefit-to-harm balance to become available to patients more rapidly is a laudable goal, the underlying question is what public health risks are taken when drugs are approved for widespread use while important safety questions remain unanswered. In its fiscal year 2011 summary, the FDA classified every new molecular entity as "innovative" and reported using 1 or more expedited approval programs for 16 of the 35 new drugs (46%).[2] All 16 of these drugs received Priority Reviews, which provide shortened review times for drugs that may offer a therapeutic advance; 13 drugs were also designated for the Fast Track program, which allows reviews to begin before clinical studies are complete for drugs that may fill serious unmet medical needs; and 3 drugs received Accelerated Approval, a program that relies on preliminary but not definitive evidence of benefit.

Three examples involving drugs for treatment of cancer, multiple sclerosis, and stroke prevention highlight the complex safety issues raised by the expedited approval pathway. These new drugs included some agents with limited clinical trial data and substantial risks.

A New Cancer Treatment

Vandetanib was approved after a single trial of 331 patients with late-stage medullary thyroid cancer.[3] Although this trial showed that vandetanib had an advantage in improving an end point of progression-free survival, the drug was sufficiently toxic that overall survival—a critical benefit—was not different from that achieved with placebo. It is questionable whether progression-free survival without improved overall survival should be an acceptable trial end point for expedited approval. A key problem, according to the FDA reviews, was that "Vandetanib caused substantial and sustained QTc prolongation, torsades de pointes, and sudden death. Even intensive [electrocardiographic] monitoring does not mitigate the risk of serious ventricular arrhythmia and sudden death."[3] Lack of sufficient clinical data left FDA reviewers uncertain whether a lower dose would reduce toxicity while maintaining efficacy. Vandetanib was approved under a restricted distribution program requiring special training for prescribers and pharmacists.

Fingolimod in Multiple Sclerosis

Fingolimod, a new drug approved in 2010 for multiple sclerosis, illustrates additional strengths and weaknesses of the FDA's innovation approach. Fingolimod suppresses the immune system through the novel mechanism of inhibiting the egress of lymphocytes from the lymph nodes. Also, fingolimod can be administered orally, whereas leading disease-modifying biologic products for multiple sclerosis, the interferons, require injections. In a 2-year clinical trial, fingolimod demonstrated an advantage over interferon beta-1a in preventing relapse of multiple sclerosis.[4]

However, the safety profile of fingolimod raises important questions about its suitability for unrestricted, first-line use. Clinical testing disclosed 7 major safety issues: adverse effects on heart rate (including complete atrioventricular block), opportunistic infections, reduced pulmonary function, liver toxicity, teratogenicity, macular edema, and possible cancer risks.[5] Drug testing in a kidney transplant population was halted because of safety concerns at the 5.0-mg and 2.5-mg daily doses. As clinical trials evaluating the multiple sclerosis indications proceeded, the 1.25-mg daily dose treatment groups of all ongoing trials were terminated for safety reasons. Thus, only the lowest of the daily doses tested, 0.5 mg, was pursued for FDA approval.

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Because all of the doses above 0.5 mg had been terminated for safety reasons, it was not surprising that the FDA Peripheral and Central Nervous System Drugs Advisory Committee unanimously voted that fingolimod should be tested at a lower 0.25-mg dose; however, the committee also voted not to delay approval. The FDA approved fingolimod for first-line use but required 10 postmarketing studies, including one at a lower dose. The European Medicines Agency restricted fingolimod to second-line use, and 3 published reviews questioned why the FDA had approved fingolimod for first-line use.[6]

Dabigatran for Prevention of Stroke

Dabigatran, the first new oral anticoagulant approved in 56 years, benefited from 3 different FDA policies promoting innovation. This drug received both Fast Track and Priority Reviews and was studied in a single large phase 3 trial rather than in at least 2 pivotal trials, as normally required.[7] Dabigatran was considered significantly easier to use than warfarin for reducing the risk of stroke in patients with atrial fibrillation, because regular monitoring is not recommended. In the phase 3 trial of dabigatran, the risk of serious bleeding was similar for the 2 drugs.[8] The FDA approved only a single primary dose of 150 mg. Unlike regulatory agencies in Canada, Japan, and Europe, the FDA did not approve a lower 110-mg dose and commented that the drug might be usefully studied at a dose higher than 150 mg.

The limitations of a one-size-fits-all strategy for a treatment as inherently risky as anticoagulation in elderly patients soon became apparent. Within less than a year of approval, 1 survey showed that dabigatran accounted for more serious adverse drug events reported to the FDA during the second quarter of 2011 than any other regularly monitored drug.[6] Risk of hemorrhage was prominent in older patients (median age, 80 years), a subgroup for whom declining kidney function or other factors may have increased bleeding risk. Both a manufacturer package insert revision and the European Medicines Agency have called for closer monitoring of kidney function, a needed step because even moderate kidney impairment increases dabigatran levels more than 2-fold. In addition, unlike warfarin, no antidote is available for use in bleeding emergencies related to dabigatran. Evidence was beginning to emerge that dabigatran-related bleeding—whether from trauma or as an adverse effect—may be more difficult to treat than warfarin-related bleeding.[9]

Conclusions

These examples raise the question of whether it was good policy to approve 3 innovative new drugs with significant safety questions unanswered and with optimal doses not determined. For patients with medullary thyroid cancer, multiple sclerosis, or atrial fibrillation who need anticoagulation, these drugs may offer benefit but with substantial risks not yet fully understood. The fundamentals of clinical testing and drug safety have not changed. It takes years of development, costly clinical trials, and extensive analyses to establish the clinical conditions under which new drugs will do more good than harm. Risks persist, even with standard approvals. Meanwhile, the US Senate, in approving a regular 5-year update to the Food, Drug, and Cosmetic Act, proposed a further expansion of expedited review, with a new category for "breakthrough drugs." For physicians, the FDA's emphasis on rapid drug approval underlines the importance of the 6 "principles of conservative prescribing" that include the warning, "Exercise caution and skepticism regarding new drugs."[10]

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REFERENCES

1. Driving Biomedical Innovation: Initiatives for Improving Products for Patients. US Food and Drug Administration website. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm. Accessed April 12, 2012.
2. FY2011 Innovative Drug Approvals. US Food and Drug Administration website. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm. Accessed April 12, 2012.
3. Justice RL. Summary Review for Regulatory Action: NDA 022405 Vandetanib. Silver Spring, MD: US Food and Drug Administration, Center for Drug Research and Evaluation; April 1, 2011.
4. Cohen JA, Barkhof F, Comi G, et al; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402-415.
5. Lourdes V, Yasuda S. Clinical Review—Safety: NDA 22-527 Fingolimod (Gilenya). Silver Spring, MD: US Food and Drug Administration, Center for Drug Evaluation and Research; August 8, 2010.
6. Moore TJ, Cohen MR, Furberg CD. QuarterWatch: Monitoring FDA MedWatch Reports: Signals for Fingolimod (GILENYA) and Infliximab (REMICADE). Institute for Safe Medication Practices website. http://www.ismp.org/QuarterWatch/pdfs/2011Q2.pdf. Accessed April 12, 2012.
7. Unger EF. Deputy Office Director Decisional Memo: NDA 22-512 Dabigatran Etexilate (Pradaxa). Silver Spring, MD: US Food and Drug Administration, Center for Drug Evaluation and Research; October 19, 2010.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
9. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med*. 2011;365(21):2039-2040.
10. Schiff GD, Galanter WL, Duhig J, Lodolce AE, Koronkowski MJ, Lambert BL. Principles of conservative prescribing. *Arch Intern Med*. 2011;171(16):1433-1440.