E. ZURGA/BLOOMBERG NEWS/GETTY

US sales of dietary supplements exceed US$28 billion a year, but ingredients are unregulated.

Strengthen and stabilize the FDA

The US Food and Drug Administration needs to be more independent, says **Daniel Carpenter**.

There is perhaps no more important public-health agency in the world than the US Food and Drug Administration (FDA). Its policies have reshaped science and regulation worldwide, giving billions of people greater confidence in the treatments and foods on which they rely[1]. Yet the agency's capacity and autonomy — and hence the services it renders — are in jeopardy.

The FDA is plagued by threats to its power and stability. A vivid example of this came last December, when the agency was shockingly overruled by Kathleen Sebelius, secretary of the Department of Health and Human Services (DHHS). She decided, with public backing from President Barack Obama, that the contraceptive drug Plan B would not be available to teenagers under the age of 17 without a prescription.

With this move, Sebelius quashed an eight-year decision process, turned back more than 70 years of precedent in which the agency's decisions are final, and invited future drug-approval contestants to take their case directly to the White House.

At the same time, the agency has little jurisdiction over a growing segment of the health-care system: dietary supplements. This regulatory gap has had deadly consequences. Today, dozens of athletic supplements sold throughout the United States contain DMAA (1,3-dimethylamylamine), a stimulant similar to amphetamine that was withdrawn from the US pharmaceutical market in the 1970s because of health concerns.

In 2010, US sales of supplements containing DMAA exceeded US$100 million. DMAA has been linked to increased blood pressure and heart rate, panic attacks, seizures and stress-induced cardiomyopathy. After two deaths last year, the US military in December stopped the sale of supplements containing DMAA on its military bases. Last summer, Health Canada banned DMAA from all supplements.

Amid such developments, many things have been going well for the FDA. The agency approved a near-record number of medicines last year[2], and it brings new cancer therapies to market quicker than its counterpart, the European Medicines Agency[3]. And the FDA has asserted its independence at times — under immense pressure to continue permitting the drug bevacizumab (Avastin) to be marketed for metastatic breast cancer, the agency instead followed the scientific evidence and revoked its approval in November 2011. (Avastin remains available for off-label prescription and for other cancers.)

The agency has also demonstrated strength and flexibility in its regulation of diet pills. It removed sibutramine (Meridia) from the markets and did not approve rimonabant (which was approved, then withdrawn, in Europe), but it has been willing to consider new evidence for the diet pill Qnexa (a mixture of phentermine and topiramate).

Still, the FDA's recent misfortunes leave room for concern. They come at a difficult time for US science, society and politics, during which the country's health sector has grown weaker. Until Congress acts to boost the FDA's strength and independence, the safety and confidence of the world's citizens — as well as medical and technical innovation — remain at risk. I propose a series of realistic reforms; they are not a panacea for the FDA or for US public health, but they could help to preserve the FDA's place as the pre-eminent regulatory agency in the world.

A STRONGER BODY

The priority in any reform is to strengthen the agency. As a first step, we should make the FDA a truly independent body. We should separate it from the DHHS and give the FDA commissioner a six-year term like that of the chair of the US Federal Reserve, to be deposed only 'for cause'. Agency responsibilities should be transferred from the DHHS secretary to the FDA commissioner, which would prevent future repeats of the Plan B events by placing all drug-approval decisions in the hands of the FDA, not the White House.

In addition, we should reform how the agency is funded. At present, the FDA is partly supported by application fees that drug companies pay each time they submit a new drug for approval. The rates and terms of these fees — or, more appropriately, taxes — are renegotiated every five years, creating an opportunity for agency critics to hold up funding until their demands are met, destabilizing drug development and consumer protection.

Negotiations with companies are conducted in secret, with citizens and safety advocates effectively excluded, and research has shown that drugs approved just before the drug-review deadline are more likely to encounter safety problems. The list of drugs that were approved under deadline pressure and then pulled from the market

J. REED/REUTERS/CORBIS

The FDA, headquartered in Silver Spring, Maryland, approved a near-record number of drugs last year.

because of dangerous side effects includes Vioxx, Bextra, Rezulin, Baycol, Trovan and Avandia (withdrawn in Europe)[4,5].

Instead of taxing new drug submissions to fund the FDA, the US government should tax the thing that benefits from the FDA's backing — pharmaceutical sales. The FDA induces great confidence in the nation's drug supply; the drug companies and citizens who benefit from that confidence should pay a small amount of revenue for it. To avoid giving the FDA incentive to approve and facilitate only blockbuster medicines, Congress could put a cap on the revenue raised from such a tax.

GREATER FLEXIBILITY

The agency's power over herbal and nutritional supplements should be strengthened. The DMAA example is not unique; every year, people in the United States spend more than $28 billion on supplements with the (mistaken) presumption that they are safe and effective. However, according to the 1994 Dietary Supplement Health and Education Act, supplements are not required to be proven effective, and any supplements on sale since before 1994 are assumed to be safe.

As Pieter Cohen, a dietary-supplements expert at Harvard Medical School in Boston, Massachusetts, has suggested[6], the United States should require testing of all dietary supplements. Exceptions should be made only for those substances that are 'generally recognized as safe'.

To strengthen drug development, we should reduce its cost for certain types of disease. I propose that we create a quicker, conditional approval system for drugs aimed at treating illnesses that are especially lethal or that constitute genuine public-health crises. This would extend and strengthen what the FDA and Congress have done for AIDS and cancer. For the diseases that public-health officials consider to be the deadliest and most undertreated (such as gastric and lung cancers, neurodegenerative diseases and some infectious diseases), phases II and III of the drug-development process could be more systematically merged.

The FDA could approve new drugs for these illnesses for an initial five-year window, with follow-up studies required before the drug could be re-authorized for another five years. This would create stronger incentives for companies to conduct post-market trials, and would push more of the high costs of phase III trials to the post-market phase, where they could be more easily covered by sales revenue.

"To fund the FDA, tax the thing that benefits from the FDA's backing — pharmaceutical sales."

Another way to facilitate drug development is to have the FDA open its data vaults. Pharmaceutical companies spend too much time chasing drug ideas that someone else has already tried, found to fail and abandoned. The FDA receives information on every clinical trial conducted, but it is prohibited from sharing data on failed drugs, and companies don't have unilateral incentives to share data.

With a modest but crucial change in federal statute, we could have a system in which data on failed drug-development projects are shared with companies and citizens, while the most sensitive information, such as how a company uncovered a biological or pharmacological mechanism of action, is kept proprietary. Knowledgeable sources in the pharmaceutical industry tell me that this step alone could reduce costs by 10–20%. Sharing data on abandoned drugs would also help to improve drug safety, by showing which drugs (and which substances and mechanisms of action) encountered safety and toxicity problems in the experimental stage.

TWENTY-FIRST-CENTURY AGENCY

To improve the public's trust in the FDA, Congress should set deadlines for the commissioner's decisions, which have been slow in recent years. When ruling on Avastin and the diabetes drug Avandia, the commissioner took at least three months to make a final decision after the vote from the advisory committee. This kind of delay looks bad, not least because the scientific opinion has been clarified, making any lag seem to be caused by the worst form of politics. Once the advisory committee has voted on an issue, the commissioner should have no more than a month to make a decision.

None of these reforms can be accomplished by the FDA alone; almost all of them would require changes to statute that can come only from the US Congress. And this gets us to the heart of the problem. Lately, the toxic polarization between Democratic and Republican lawmakers — and the micromanaging tendencies of Barack Obama and former President George W. Bush[7] — are damaging US public-health infrastructure and its scientific prospects, weakening one of the republic's most vital institutions. A robust FDA for the twenty-first century demands selective strengthening of the agency and flexibility on key dimensions. ■

Daniel Carpenter *is Allie S. Freed Professor of Government at Harvard University, Cambridge, Massachusetts 02138, USA, and a visiting researcher at the Institute for Political Studies at the University of Strasbourg, Strasbourg F-67081, France. e-mail: dcarpenter@gov.harvard.edu.*

1. Carpenter, D. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton Univ. Press, 2010).
2. US Food and Drug Administration. http://go.nature.com/gtnheq (2011).
3. Roberts, S. A., Allen, J. D. & Sigal, E. V. *Health Affairs* **30,** 1375–1381 (2011).
4. Miller, J. D. *J. Am. Med. Assoc.* **302,** 189–191 (2009).
5. Carpenter, D., Chattopadhyay, J., Moffitt, S. & Nall, C. *Am. J. Polit. Sci.* **56,** 89–114 (2012).
6. Cohen, P. A. *N. Engl. J. Med.* **361,** 1523–1525 (2009).
7. Harris, G. White House and the FDA Often at Odds. *New York Times* (3 April 2012).