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Perspective

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Scott Gottlieb and the Credibility of U.S. Therapeutics

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President Donald Trump has nominated Scott Gottlieb as U.S. Commissioner of Food and Drugs. The Trump administration's approach to the Food and Drug Administration (FDA) is guided

by a libertarian belief in markets over science, and Gottlieb apparently shares this view. He has argued that the agency displays an "unreasonable hunger for statistical certainty" and a "profound lack of confidence in the ability of doctors to make careful judgments." He seems poised to weaken phase 3 testing requirements.¹ The administration considered nominees with even more extreme views, including the belief that the FDA should not be in the business of regulating drug efficacy.¹

Gottlieb would differ starkly from previous FDA commissioners in two critical ways. First, though he's been a practicing physician, his previous experience in academic medicine, applied science, and government service is thread-

bare. He held a few different positions at the FDA and the Centers for Medicare and Medicaid Services during the George W. Bush administration and was appointed deputy commissioner of the FDA in 2005. Observers (including a former editor of the *Journal*) were puzzled when he ascended to deputy commissioner, because his experience had been dominated by investment advising, including as editor of the "Forbes/Gottlieb Medical Technology Investor."² His principal writings consist of essays in newspaper and think-tank policy outlets. By contrast, previous commissioners came to the agency with scientific, academic, or government experience. For more than a century, the FDA has been led by

commissioners with a primary background in science or in public health, and usually both.³

Second, Gottlieb has been enmeshed in highly remunerative relationships with the biopharmaceutical industry, including sitting on various corporate boards. As FDA deputy commissioner, he repeatedly had to recuse himself from decisions involving companies from which he'd received payments.⁴ This conflict-of-interest list has only grown in the past decade. Although the most recent commissioner, Robert Califf, was also scrutinized for possible conflicts, his industry ties were research-based, growing out of his expertise in academic cardiology and clinical trials management. Gottlieb seems unlikely to have earned his corporate-board perches with scientific expertise.

Gottlieb's background places the agency, and the public, in a difficult position. Controversy has occasionally arisen over commis-

sioners' actions — for example, Mark McClellan's rejection of his staff's recommendation to allow over-the-counter access to the emergency contraceptive Plan B, or David Kessler's spearheading of efforts to regulate tobacco products as nicotine-delivery devices. Yet past commissioners all brought to the position scientific or public credibility and dedication to the agency's core mission.

FDA commissioners rarely enter directly into deliberations about approving a drug or device. But until now, when the FDA has put its imprimatur on a product, physicians, patients, and investors knew that an agency led by an official with scientific expertise and managerial experience had scrutinized and validated those claims. That representative was never someone whose career had depended on investing in drugs without studying them scientifically.

It seemed clear from Trump's short list for commissioner that the primary qualification was not scientific acumen, public health credentials, or a successful career in biopharmaceutical science and innovation, but rather an ideological commitment to creating a "free marketplace" of therapeutics.¹ But by ensuring our safety and the effectiveness of treatments, the FDA's approval of products provides a foundation for confidence in our entire medicine cabinet.³ Our health system depends on the shared belief that drugs and devices work as advertised, that mechanisms invisible to the eye nonetheless cause healing. The underpinnings of this belief are that "somebody out there" has tested these products and shown, with at least some scien-

tific evidence, that they work as claimed.

To these arguments libertarians reply — on the basis of no evidence and a misunderstanding of health economics — that "good" products will eventually crowd out "bad" ones, that the error of releasing dangerous products is "self-correcting," whereas the sin of delaying a product's availability is not. (The surge of patient advocacy in the past three decades greatly undermines this latter claim.³)

Yet health systems and therapeutic markets will never work that way. The process of determining interventions' therapeutic value is difficult and fraught with biases. Patients can be "cured" of some conditions through placebo effects, and natural remission of other diseases (self-limiting infections, waxing and waning depression) can interfere with efforts to study an intervention's effects. In clinical practice, patients self-select into treatments, but comparing one therapy to another to determine its value requires experimental controls; otherwise, we are left with massive biases in our evidence base.

Combined with heavy advertising and faults in our insurance system — Medicare's guaranteed coverage for FDA-approved drugs and the separation of prescribing from payment — these biases have resulted in highly profitable markets for dubious products. Patent medicines enjoyed a \$2 billion market in 1950; today's market for health supplements reaches into the tens of billions of dollars. About 75,000 Americans used the false cancer therapy Laetrile at the peak of its popularity.³ The human costs of these products ex-

tend far beyond money misspent. They include good treatments forgone and forfeited market share for truly effective therapies.

The controlled clinical trials that demonstrate therapies' average treatment effects — and increasingly generate rich evidence on subpopulations — provide the best attainable evidence that drugs and devices are trustworthy. The now-global system of phased clinical trials that delivers this evidence is largely an American invention, and other countries continue to embrace it.³ India, China, Australia, and Europe have been strengthening their testing requirements for medicines. What will happen when those societies begin to question, legitimately, the value of little-studied American medicines and devices?

Testing requirements also ensure that small biopharmaceutical firms can compete with large drug companies on the basis of science and their products' therapeutic value. Eliminating efficacy and testing requirements will lead to a marketplace in which our knowledge about therapies is based not on science but on advertising. The winners will not be the small biotechnology firms where important therapeutic advances are being made, but large conglomerates with formidable marketing budgets.

Some of Gottlieb's ideas would undermine this credibility by injecting overtly political considerations into drug approval. He has proposed that "a body of politically appointed (and therefore politically accountable) officials . . . ultimately [decide] on whether a new drug should be approved. . . . If FDA reviewers were relieved of the political con-

Questions for Scott Gottlieb.

- You will have to recuse yourself from decisions about certain companies' products because of conflicts of interest. How many companies, and which ones?
- You have argued that there are "interim endpoints that can be used to more quickly gauge a medicine's benefit." Under your leadership, how would the agency commit to restricting the use of a drug or removing it from the market if later-stage evidence turns out to present a much weaker benefit profile?
- You have argued that the FDA has an "unreasonable hunger for statistical certainty." How, then, do you explain the fact that the FDA approves new drugs and devices more quickly than any other regulatory agency? Do you see accelerated approval, compassionate use, and breakthrough designations as inadequate, and if so, why?

sequences of final approval decisions, they would have more confidence and freedom to innovate in how they measure risk and benefit."⁵ Drug approval would become a political, even partisan, ball game, since decisions would rest with officials who can be directly and immediately fired by the President. American insurers and other countries would rightly view these decisions with suspicion, as would FDA staff (who might well become more cautious, not less).

To be sure, there is room for regulatory change, including possible systems of conditional approval, in which new drugs are authorized for use in smaller markets while remaining in clinical trials, giving sponsors a revenue flow and generating externally valid evidence to complement internally valid trials. The FDA has considered alternative trial designs, including possibilities for incor-

porating "real-world evidence" — meaning not what deregulatory libertarians want it to mean (testimonial evidence or uncontrolled-use studies), but rather randomized, controlled trials implemented within an administrative health system. The agency has demonstrated far more flexibility than libertarian critics have grasped.

U.S. physicians should be worried that the new administration will usher in a world where therapies depend for their trust on advertising budgets and hearsay, not scientific evidence. When drugs' scientific credibility wanes, patients may place less trust in medicines and physicians alike. Moreover, any weakening of efficacy standards will also weaken safety criteria, insofar as important safety information emerges in phase 3 studies.

The medical community and the Senate should greet this nomination with scrutiny. To this end,

I propose some questions for Gottlieb (see box). Perhaps the most important is one that can be answered only by his behavior: Will Gottlieb, if confirmed, listen more to FDA scientists or to his Trump administration superiors, corporate-board colleagues, and think-tank associates? At stake is not just the FDA, but the scientific regime of clinical pharmacology and the credibility of American therapeutics.

For another view of the FDA commissioner nominee, see the Perspective by Chandra and Sachs.

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