Op-Ed

Déjà Vu at the FDA

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AS THE DONALD J. TRUMP ADMINISTRATION TAKES OVER IN Washington, DC, the US Food and Drug Administration (FDA) finds itself in a strange predicament. On the one hand, the agency remains the world's gold standard for drug approval, conducting reviews more thoroughly and faster than any other regulatory agency in the world. The recent approval of a breakthrough genetic treatment for spinal muscular atrophy, for example, occurred just several years after the basic science discoveries and only about 3 months after the application was filed.

On the other hand, at the same time, a growing number of Americans seem to be questioning why we have an FDA that evaluates medications in depth at all. More than half the states have passed "right to try" laws seeking to give terminally ill patients greater access to medications that have passed Phase 1 testing for safety. Over the FDA's objections, judges have been interceding to provide patients' access to dubious treatment. The belief that the FDA is standing between patients and miraculous cures also appears to be gaining traction in the White House.

For the FDA, in the immortal words of Yogi Berra, "It's like déjà vu all over again." Today's FDA skeptics are hardly the first to question the agency's role. But they are the most resistant to evidence that the FDA's expertise is essential to clinical care.

When the tiny Division of Chemistry inside the US Department of Agriculture began to pay attention to treatments sold in the late 1800s, bold claims (such as "germ, bacteria, or fungus destroyer") and individual patients' stories, known as "testimonials," were the cornerstones of marketing. Even after President Theodore Roosevelt signed the Pure Food and Drugs Act in 1906, which targeted adulterated and misbranded products, the misleading marketing persisted.

[Corrections added on 25 April 2017, after first online publication: Dr. Frances Kelsey's name has been corrected in this article, and "In the early 1980s" has been changed to "In the late 1980s" in the third last paragraph of this article].

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Frustrated officials at the agency—by then, known as the FDA—developed a traveling road show called the Chamber of Horrors. One part of the exhibition presented copies of testimonials from patients with diabetes thanking the manufacturer of the remedy Banbar for saving their lives—right next to the death certificates of the same patients several months later.

In 1938, the nation was stunned by the poisoning of scores of Americans from Elixir Sulfanilamide, an early antimicrobial that a manufacturer had sold without safety testing. In response, Congress passed, and President Franklin Roosevelt signed, the Food, Drug, and Cosmetic Act, which authorized the FDA to conduct a safety review prior to sale. The law also empowered the FDA to obtain a court order to stop companies from making claims that could be demonstrated to be false. The FDA struggled, however, to make use of its new power to protect the public, largely because it proved difficult to counter the stories of individual patients. Walter Campbell, the FDA commissioner, complained that “testimonials may be obtained for practically any article labeled as a treatment for practically any disease.”¹

One of the early controversies of this era was a cancer treatment developed by William Frederick Koch, a professor at the Detroit College of Medicine.² From the 1920s to the 1940s, Dr. Koch and his associates treated thousands of patients with a product that was little more than distilled water. When the agency attempted to take action in court, witnesses for Koch told story after story of patients who dramatically improved. The case ended in a deadlocked jury. So did the retrial.

In the early 1950s, Dr. Andrew Ivy from the University of Illinois College of Medicine claimed a breakthrough against cancer with a compound called Krebiozen.³ Despite negative reviews from the American Medical Association and other independent scientists, many patients, journalists, and legislators called Dr. Ivy the “underdog innovator” and demanded patients’ access.

As the Krebiozen controversy percolated, the nation’s attention was diverted by the shocking story of thalidomide, a product developed in West Germany and used for sedation and for nausea during pregnancy. In late 1961, it became evident that thalidomide was associated with a wave of severe birth defects across Europe. Yet thanks to the diligence of reviewer Dr. Frances Kelsey and the support of her supervisors, the FDA never approved thalidomide for sale in the United States. In the wake

of this tragedy, Congress passed landmark legislation in 1962 requiring companies to demonstrate the effectiveness of their products to the FDA before marketing them.

Yet the FDA had trouble enforcing these new data requirements. In 1965, the FDA took Dr. Ivy to court to challenge the marketing of Krebiozen. The case lasted for 8 months, with nearly 200 witnesses telling stories of miraculous cures. In yet another loss for the FDA, Dr. Ivy was acquitted.

In the early 1950s, Dr. Ernst T. Krebs began to sell Laetrile, a purported cancer cure extracted from apricot seeds that failed in its early clinical trials. Nevertheless, after hearing testimonials, multiple state legislatures passed laws permitting the use of this unapproved drug by terminally ill patients. According to historian James Harvey Young, “State legislators had their own problems with the powerful federal presence, and might listen with sympathy to constituents blasting segments of the Washington bureaucracy.”⁴ The FDA repeatedly lost in court before finally prevailing in a 1979 decision by the US Supreme Court, which rejected the right to use unapproved drugs.

Soon after this landmark case, however, the HIV epidemic turned the spotlight back to the FDA’s role in the pharmaceutical market. In the late 1980s, AIDS activists, such as the advocacy group AIDS Coalition to Unleash Power (ACT-UP), assailed the agency for blocking access to potentially lifesaving therapies. Quickly, however, leading advocates recognized the value of evidence. When advocates, researchers, manufacturers, and the agency began working together to accelerate high-quality studies, great advances in science and clinical care resulted.

Now, in the era of personalized medicine, the FDA’s old is new again. Charismatic clinicians are promising breakthroughs from stem cells and other regenerative treatments; while many are entranced by individual stories, the FDA is asking to see the data. There is an American tendency to equate scientific review with bureaucratic delay. But it is this review that distinguishes what works from what does not and that orients the pharmaceutical market toward meaningful benefits for patients instead of hype. Ironically, the growing threats to the FDA are happening at a time when the agency’s expertise is especially needed.

Given the agency’s history, the latest attacks on the FDA cannot be called surprising. After all, as early as 1894, Dr. Harvey Wiley, the agency’s first leader, noted: “To be cheated, fooled, bamboozled,

cajoled, deceived, pettifogged, hypnotized, manicured, and chiropidized are privileges dear to us all. Woe be to that paternalism in government which shall attempt to deprive us of these inalienable rights.”⁵

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