Califf takes the helm at the US FDA, again

Robert Califf will have to face several controversial health issues in his second tenure as commissioner. Susan Jaffe reports from Washington, DC.

After 13 months and two COVID-19 surges, the US Food and Drug Administration (FDA) finally has a permanent commissioner: Robert Califf. A widely respected cardiologist and researcher, Califf returned for his second spell at the agency last month. But, if his very slim approval margin from the US Senate is any indication, navigating a way forward will not be easy, even for someone who has been commissioner before.

Califf was the FDA's deputy commissioner for medical products and tobacco when then-President Barack Obama nominated him for the top job in 2016. The Senate approved his nomination by a vote of 89 to 4. He was commissioner for nearly a year until Donald Trump became president. Califf then resumed his work as a professor of medicine at Duke University (Durham, NC) and later became director of the Duke Translational Medicine Institute. He left Duke in 2019 to become a senior adviser for Verily Life Sciences and Google Health and has also had ties with pharmaceutical companies. After President Joe Biden nominated him, a less friendly Senate supported Califf last month by a margin of just four votes. Califf earned the support of Massachusetts Democratic Senator Elizabeth Warren by assuring her that he would not work for the pharmaceutical industry for at least 4 years after leaving the FDA. Six Republicans joined the Democrats to cast 50 votes for him, barely offsetting the loss of five Democrats who sided with the Republican opposition, casting a total of 46 votes.

Califf takes over amid a lull in the COVID-19 pandemic and an array of hotly debated issues 9 months before a congressional election. The election results could shrink, if not eliminate, the Democratic majority Biden needs to propel his health agenda, including the relaunched cancer moonshot and the Advanced Research Projects Agency for Health that would accelerate the development of medical treatments.

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"I think Rob Califf is the right person at the right time," for the FDA, said Ellen Sigal, chairperson and founder of Friends of Cancer Research, a patient advocacy organisation. "To me, Dr Califf checks all the boxes," said Steven Grossman, executive director of the Alliance for a Stronger FDA, a coalition of 150 consumer, patient, and industry groups. "He has intimate knowledge of the agency. He understands how medical products are developed, tested, and proven. He comes from an academic medical background, rather than an industry background. He's been a clinician, helped run clinical trials, and has been deeply involved in the movement to make clinical trials better. I think he's got all the right credentials."

The FDA is responsible for the safety of a wide range of products that represent about 20% of all US consumer spending, around US$2·7 trillion last year. These include artificial hips, dietary supplements, gene therapy, surgical lasers, prescription drugs for both humans and animals, nanotechnology products, cosmetics, blood and biological products, tobacco and electronic cigarettes, and most of the domestic and imported food that Americans eat (except for meat and poultry, which falls under the purview of the US Department of Agriculture).

In addition to managing these operations, Califf must deal with urgent matters, such as how to quickly develop COVID-19 treatments and tests, and faces pressure to reduce the number of deaths due to opioid misuse, contend with states that have defied the FDA's medication abortion policy, and help the cancer moonshot programme reach its goal of cutting cancer deaths by half within 25 years.

Furthermore, the FDA's controversial proposed regulations prohibiting menthol in cigarettes—the only flavour still permitted—and all flavours in cigars moved one step closer to finalisation when it was submitted to the Office of Management and Budget for review last month. Removing menthol from cigarettes could prompt more than 900 000 Americans to stop smoking, according to a study that the FDA cited when it announced the proposals last year.

Although this daunting agenda demands adequate staffing, recruitment continues to be a problem. The Biden administration has expanded the FDA workforce from roughly 15 875 people in 2018 to around 18 840 this year; however, the agency currently has approximately 1775 vacancies, according to an

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FDA spokesperson. To boost job applications, the FDA last year placed advertisements in the Washington DC area subway and train system, encouraging job seekers to "make a difference" by joining the FDA.

The COVID-19 pandemic

Around 75% of US adults are fully vaccinated against COVID-19 and in most parts of the country, the prevalence of COVID-19 cases is low (at least for now). According to the Centers for Disease Control and Prevention, as of March 10, 98% of Americans live in areas where wearing masks in public indoor spaces is optional (masks are still required when using public transport). Nevertheless, parents are still waiting for the FDA to approve a COVID-19 vaccine for children younger than 5 years. After cancelling a meeting last month to discuss the merits of a three-vaccine regimen for this age group of children, the agency postponed its decision until additional data could be evaluated.

The COVD-19 pandemic is priority "number one," Califf told the Senate Committee on Health, Education, Labor and Pensions during its December hearing on his nomination.

"I'm fully aware of the need for the FDA to help develop platforms that will be essentially ready to go when emergencies come up," he testified. But that process must include "the right balance of protecting Americans in a safe way, and being innovative in the development of products that can move along quickly. An essential in that priority is the development of a better evidence generation system."

Opioid misuse

At his nomination hearing, several senators criticised Califf for not doing enough to control opioid misuse during his first stint as the FDA commissioner and asked him what should be done now. Califf told the committee chair, Washington state Democratic Senator Patty Murray, that better prescriber education and alternative pain medications were necessary, in addition to cracking down on physicians who overprescribe painkillers. New Hampshire Democratic Senator Maggie Hassan asked if the FDA had made a mistake in 2001 when it revised the OxyContin label to indicate that the drug was safe when taken for an extended period of time. Califf said that he disagreed with "only a little part" of that decision. He said there was insufficient evidence at the time to support it. "I'm an evidence-based person, and if we're going to instruct people to take drugs for long periods of time, we need long-term studies," he said. Hassan then asked if the label should be corrected. "I think as the evidence comes in, we are going to need to aggressively look at relabelling", Califf said.

Califf's responses did not persuade Hassan and four other Democratic senators that the FDA would do enough to stop opioid misuse and prompted them to vote against his nomination.

Accelerated drug development

Califf also fielded questions about how to speed up patient access to new drugs without compromising safety and efficacy. "More than 265 treatments and therapies have been approved under the accelerated approval pathway and have made a marked difference in cancer treatment," North Carolina Republican Senator Richard Burr told Califf. Burr sought Califf's commitment not to slow down the process.

Califf said that he supported accelerated approval for some health conditions. "I've spent countless hours with patient groups, people with rare genetic diseases, cancer, serious diseases for which there's no treatment," he said. But accelerated approval also "means that we're accepting that there's more uncertainty…we've got to have a better system to evaluate these products as they're used on the market". Shortly before the full Senate approved his nomination, Oregon Democratic Senator Ron Wyden announced he would support Califf after receiving his assurance that the FDA would strictly monitor drug companies whose products receive accelerated approval. "FDA must ensure that drug developers granted accelerated approval conduct confirmatory studies that demonstrate that the balance of clinical benefits and risk for intended use of the drug is positive, and this must be done in a timely manner," Califf wrote in a letter to Wyden.

Abortion pill

Another issue expected to demand Califf's attention is the FDA's decision in December, 2021, to remove a requirement that women using a drug called mifepristone to induce an abortion could only take it in a doctor's office, clinic, or other health-care setting. The decision extended a temporary pandemic-related measure that allowed the drug to be mailed to women or prescribed via telehealth appointments and then picked up at pharmacies. Last month, the Guttmacher Institute (New York, NY) reported that medication abortions accounted for 54% of all US abortions in 2020.

The new policy puts the FDA on a collision course with nearly two dozen states that mandate in-person abortion procedures. More states are likely to enact similar restrictions on the FDA-approved drug if the Supreme Court issues a decision later this year to modify or even overturn the court's landmark 1973 *Roe vs Wade* ruling, which guaranteed a woman's right to abortion.

States cannot set rules that are more restrictive than a federal law or regulation, but what happens when they do exactly that "is an underdeveloped area of law," said Mary Ziegler, a professor of law at Florida State University College of Law (Tallahassee, FL) and an expert in the legal history of abortion. "This is uncharted territory."

Susan Jaffe