A Threat to Evidence-Based Vaccine Policy and Public Health Security at the FDA

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As former commissioners of the U.S. Food and Drug Administration (FDA) — who collectively guided the agency's oversight for more than 35 years, through myriad public health crises — we are committed to medical product safety and identifying new medical evidence with the speed, rigor, and openness that the public should expect. We are deeply concerned by sweeping new FDA assertions about vaccine safety and proposals that would undermine a regulatory model designed to ensure that vaccines are safe, effective, and available when the public needs them most.

The existing regulatory model builds public trust by encouraging open information exchange and rigorous, transparent scientific debate. Yet a memo sent last week to FDA staff will upend core policies governing vaccine development and updates.[1] These measures, and the unilateral way they are being imposed, undermine the public interest. They are the latest in a series of troubling changes at the FDA, including substantial departures of FDA staff, that could diminish both the FDA's strength and Americans' health and safety.

The memo (available at https://www.biocentury.com/article/657740) was written by Vinay Prasad, director of the FDA's Center for Biologics Evaluation and Research (CBER), who also serves as the agency's chief scientific officer, chief medical officer, and acting head of CBER's office of biostatistics, as well as overseeing the division responsible for vaccine review and approval. His memo characterizes the actions of FDA scientists who express concerns about agency processes or decisions to outside parties as "unethical" and "illegal." It calls for scientific debates to be kept within the agency "until they are ready to be made public," and instructs staff members who disagree with the new framework to "submit your resignation letters."

The proposed guidelines would dramatically change vaccine regulation on the basis of a reinterpretation of selective evidence and by a process that breaks sharply with the norms that have an-

chored the FDA's globally respected scientific integrity. If enacted, the framework would impede the ability to update vaccines to keep up with the natural evolution of respiratory viruses or changes in the prevalence of bacterial serotypes; it would also suppress innovation and competition. The net effect would be to disadvantage the people the FDA exists to protect, including millions of Americans at high risk from serious infections.

The new framework rejects the agency's long-standing reliance on "immunobridging" studies for well-understood vaccines with extensive safety data. Using this approach, once a reliable correlation with effectiveness has been established, a vaccine's ability to stimulate the immune system to produce protective antibodies can serve as a surrogate for its efficacy in helping patients avoid infections and complications from rapidly evolving viruses such as SARS-CoV-2 and influenza. Because these viruses change frequently, repeating large-scale efficacy trials for every new seasonal strain is not feasible within the time needed to update the vaccines. Bridging studies have also been used to broaden vaccine protection to additional serotypes of bacteria.[2] The FDA continually updates the correlate strains used for immunobridging studies to ensure that vaccines remain safe and effective as threats evolve. Immunobridging studies have also been used for some new products, including the human papillomavirus vaccine that could largely eliminate cervical cancer.

The proposed new directives are not small adjustments or coherent policy updates. They represent a major shift in the FDA's understanding of its job. The memo states that "no amount of cell or humoral mediated immune surrogates" can justify approval of new or updated vaccines — logic that Prasad claims is implied by the lack of a full biosimilar pathway for vaccines. These arguments misrepresent both the science and the regulatory record, especially in the case of vaccines that target well-understood pathogens through an established mechanism of action.

Abandoning the existing methods won't "elevate vaccine science," as the memo asserts. It will subject vaccines to a substantially higher and more subjective approval bar. The proposed measures will slow the replacement of older products with better ones and will create potentially prohibitive expenses for new market entrants, especially small biotechnology companies. It's true that vaccines can generate substantial profits and that their complexity thwarts true generic competition, as the memo observes. But the proposed policy response would reduce competition and raise prices by demanding premarketing randomized clinical trials "for most new products."[1,3] Moreover, insisting on long, expensive outcomes studies for every updated formulation would delay the arrival of better-matched vaccines when new outbreaks emerge or when additional groups of patients could benefit. It is important to create a clear, science-driven, and well-reasoned pathway to approval; otherwise, innovators will have no reliable way to design their development programs. The people most affected by the FDA's proposed framework will include older Americans and those with weakened immune systems who rely most on the protection that timely and updated vaccines can offer.

The new approach would also evade public transparency, including long-standing statutory and regulatory mechanisms that enable disagreements about benefit–risk balance, clinical trial end points, trial design, and data analysis to be aired in public. Under the Administrative Procedure Act and the FDA's Good Guidance Practices, changes of this magnitude should be developed by guidance or regulation, with broad consultation within the agency, meaningful opportunity for public comment, and often public advisory-committee input. The FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) exists precisely so that controversial scientific and policy questions receive independent expert review in public. Yet FDA Commissioner Martin Makary's leadership team has said they intend to forgo advisory committee meetings for many major decisions, since they view these committees, which were established by bipartisan agreement in Congress decades ago, as a needlessly costly and burdensome check on their decision making.[4]

The stated motivation for these sweeping changes is the deaths of 10 children, which the FDA leadership asserts were caused by Covid-19 vaccines. Any death that could be related to vaccination is tragic and warrants extensive investigation. Previously, all the cases reported to the Centers for Disease Control and Prevention (CDC) and to the FDA had been carefully reviewed by FDA staff, who drew different conclusions. Adjudication of individual case reports is sensitive and subjective, and it

relies on the rigor and goodwill of the people doing the evaluation. The memo offered no explanation of the process and analyses that were used to reach the new retrospective judgment, nor did it indicate why that assessment should justify wholesale rewriting of vaccine regulation.[1]

The reanalysis relied on adverse event reports filed in the Vaccine Adverse Event Reporting System (VAERS), a passive post-approval surveillance system that collects unverified reports, from any source, of events occurring after vaccination. VAERS reports, by themselves, cannot be used to determine whether a vaccine caused a particular event. The system's primary purpose is to flag potential safety signals that must then be evaluated in carefully designed investigations. VAERS data have well-recognized challenges, including reporting bias and a lack of control groups.[5] The FDA therefore relies on many other data systems and methods as well, including medical record review, active surveillance programs, and independent peer review.

Yet accepting the review of VAERS reports as proof that "no fewer than 10" deaths were caused by Covid-19 vaccines, Prasad concludes that the vaccines caused net harm in children — and then seeks to justify sweeping changes in regulatory standards for Americans at much higher risk for complications from many other infectious diseases. All vaccines have risks and benefits, which are clarified by careful, transparent evaluation of evidence; FDA communications should present risks and benefits in a balanced manner. But the benefits and risks of many established vaccines are well understood, and imposing the new approval requirements without meaningful new evidence could make it impossible to keep up with evolving infectious threats.

The memo asserts, incorrectly, that "we do not have reliable data" on the benefits of Covid vaccination in children. Reasonable scientists should engage in open debate about how best to shape recommendations for children at lower risk for Covid-19, but substantial evidence shows that vaccination can reduce the risk of severe disease and hospitalization in many children and adolescents.

Of course, the FDA must be willing to reexamine the standards for approval when new data warrant change. Such conversations, however, must also adhere to the process that gives FDA decisions their legitimacy: open deliberation and robust engagement with the agency's staff and the broader community. Scientific disagreements should be respected. Demands for ideological alignment as a condition of employment are irreconcilable with an agency whose strength is the pluralism of its expert views. Americans' safety depends on a culture in which evidence is reviewed openly and staff can surface concerns, challenge leadership, and engage with external scientists without fear of reprisal.

The FDA has helped save millions of lives, sharpening its judgment as new evidence and better methods were developed, debated, and refined. Working at the FDA under both Republican and Democratic administrations, we saw up close how deeply the agency's staff believed in its public health mission. If the goal is to rebuild confidence, the answer is not to toss aside the basic rules of science, stifle argument and oversight, or supplant expert scientific inquiry for the unilateral decision making of a few individuals. It is to insist on open deliberation, solid evidence, and procedures the public can see and trust.

Disclosure forms provided by the authors are available at NEJM.org.

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