Subcommittee on the Administrative State, Regulatory Reform, and Antitrust of the Committee on the Judiciary

Hearing on: "Follow the Science?: Oversight of the Biden Covid-19 Administrative State Response"

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Introduction

My name is Philip Krause, and I appreciate the opportunity to testify at this hearing. I also am grateful to the Committee for making available the transcript of my September 7, 2023 transcribed interview[1].

I worked at the FDA from 1991 to 2021 in various roles, the last ten years of which I served as Deputy Director of the Office of Vaccines Research and Review (hereafter, Office of Vaccines or OVRR) in FDA's Center for Biologics Evaluation and Research. Importantly, I have worked in many different roles at the FDA so have seen the regulatory process both from the perspective of an individual reviewer and a leader, both as a civilian and as a US Public Health Service Commissioned Officer. In addition to an MD degree from Yale University, I have a Masters of Business Administration from Florida State University, a Masters of Science degree in Computer Science from the University of Illinois, and a Bachelors of Science degree in Mathematics and Computer Science from the University of Illinois. After graduating from medical school, I performed a residency in Internal Medicine at University Hospitals of Cleveland (affiliated at that time with Case Western Reserve University) and a fellowship in virology and infectious diseases at the National Institutes of Health. I am board-certified in Internal Medicine and Infectious Diseases. Over my career, I have published over 100 peer reviewed articles in fields spanning regulation, vaccinology, clinical trials, virology, epidemiology, vaccine safety, and even biostatistics. I also have been on the Scientific Advisory Committee for CEPI (a non-profit seeking to accelerate development of vaccines and countermeasures against epidemic and pandemic threats) since 2017.

During the COVID pandemic, I was the highest-ranking infectious diseases physician in the Center for Biologics. Along with the Office Director, Dr. Marion Gruber, I helped to supervise the review activities related to COVID vaccines. This included substantial contributions to guidance

[1] https://judiciary.house.gov/sites/evo-subsites/republicans-judiciary.house.gov/files/2024-06/2024-06-24%20Politics,%20Private%20Interests,%20and%20the%20Biden%20Administration%E2%80%99s%20Deviation%20from%20Agency%20Regulations%20in%20the%20COVID-19%20Pandemic%20%5bwith%20Appendix%5d.pdf

documents and policy development. In addition to other duties, I was assigned as a liaison to WHO, where I became the chair of the WHO COVID vaccine expert working group

Since I left the FDA in 2021, I have worked as an independent consultant, which has included providing advice to the WHO and to various biotechnology and pharmaceutical companies.

Background on FDA and Regulation

The US Public Health system is based on trust in government officials tasked with making benefit/risk decisions regarding products to prevent serious and life-threatening infectious diseases, and the review process they implement to assure the safety and effectiveness of drugs and biological products. Of concern, trust in Federal public health agencies declined through the pandemic. A KFF survey performed over time showed reducing trust in public health agencies between December 2020 and April 2022[2], with the most dramatic reductions in trust occurring among Republicans. Another study reported that reasons for lost trust were conflicting recommendations and perceptions of political influence, along with perceptions that agencies recommendations went too far and declining trust in government[3]. At this point, this reduced trust is leading to concern about vaccine hesitancy even for established childhood vaccines[4].

Regulatory agencies, in part, exist in order to provide objective evaluations of fact. If the public loses trust in the Agencies, it becomes impossible for the Agencies to fulfill one of their primary missions—which is to be a source of trusted information to the public. For the FDA, this information includes the assurance that regulated products will be safe and effective. In general, trust can be enhanced by objectivity, adherence to standards, adherence to process, and transparency. And under normal circumstances, the system is set up to promote trust in all of these ways. However, in a pandemic, significant risks to trust can arise.

The major Federal Agency contributors to vaccine policy are the FDA and the CDC. Other agencies also make contributions, but the FDA is at the center of this, because FDA both determines which vaccines (or other FDA-regulated products, including all medical products, for that matter) can be marketed, and FDA serves as an independent and objective reviewer of fact, to assure that the manufacturers' claims are accurate and supported by the data. The package insert (or in the case of an EUA, the fact sheet) sets out the claims that FDA has verified, and this limits the claims that a manufacturer is allowed to make about the product while marketing it. Once the FDA has decided to make a vaccine available to the public, policy decision-making and recommendations about how to use that vaccine are up to the CDC, with the strong advice

[2] https://datawrapper.dwcdn.net/A0mdU/3/
[3] https://www.eurekalert.org/news-releases/981648
[4] https://time.com/6564694/measles-antivaccine-misinformation/

of its Advisory Committee on Immunization Practices (ACIP). By separating decisions about approving and using vaccines, a major potential intellectual conflict of interest can be avoided, because if the same body approved, recommended, and had the authority to revoke the approval of a vaccine, one could imagine that body being reluctant to take action as quickly if problems arose during usage. Indeed, the ACIP tends to be a strong advocate for vaccine usage based on their public health benefit, while the FDA generally limits its opinions to objective evaluation of the safety, efficacy, and manufacturing data that it reviews.

This is just one of the ways in which the system, when it is working, helps to promote trust in vaccines. FDA reviewers are not allowed to have any conflicts of interest with respect to the regulatory work they do, and are subject to some of the strictest ethics rules in government, which also cover financial holdings and disclosures.

The Office of Vaccines has responsibility for all vaccines intended to prevent infectious diseases. A typical review effort includes reviewers from different disciplines, who each bring their own expertise. Supervisors are needed to manage the review workload and to help assure consistency in review standards across different products.

At the Office level, we coordinated the reviews across relevant review disciplines, liaised with other Offices when needed, coordinated advisory committee meetings and other external engagements including vaccine-specific press inquiries, contributed to regulatory policy, initiated and coordinated the writing of product-specific guidance documents, and provided an additional layer of assurance that similar and appropriate standards, consistent with the regulations, were applied to all of the products the Office was responsible for reviewing.

At FDA, the Office is the highest level tasked with ensuring the safety and efficacy of products under its jurisdiction that is based on specialized technical expertise. The public can have confidence that scientific and technical decisions made at the Office level are correct based on the large number of trained expert reviewers who have contributed and reached agreement on regulatory decisions. In addition, for many reviews, outside input from an expert advisory committee—for vaccines this is the Vaccines and Related Biological Products Advisory Committee (VRBPAC)-- is also solicited. Because of the large number of discussions between subject matter experts and supervisors and the opportunity for this outside input, most reviews end with a broad consensus regarding what to do. Occasionally, though, there would be some disagreement (usually not because one person was wrong and one was right, but because they may have approached a problem from different perspectives), and it would be necessary for the Office Director to determine which reviewer's perspective was most closely aligned with the Agency's mission. Although the Office Director had the authority, I don't remember a single instance in which the Office overruled an entire review team.

Under normal circumstances, the entire review takes place within the Office. Officials, including the Center Director, at higher levels are kept informed so that if there were concerns about how consistently review standards were applied across products, they could be addressed, or if there were disagreements between stakeholders in different Offices, they could be addressed. In each Center, the Director has oversight for disparate products, and thus does not typically possess the specialized expertise of the product Offices. The Center Director's office also has responsibility for budget and management of the workforce, and overall priority setting.

While the Center Director's office has the authority to overrule an Office on a specific regulatory decision, exercise of that authority should almost always be based on the need to assure consistent application of regulatory standards. Technical disagreements with a review team should almost never be the basis for overruling an Office (which represents the entire review team)—because the Office is designed to contain more (and more specialized) technical expertise than the Center Director and has had the benefit of many internal discussions and adherence to a process that has been developed to result in technically valid decisions. Although the Center Director, as an individual has the authority to overrule on any grounds, overruling an Office team on technical grounds is almost certain to reduce confidence in the FDA. First, does this mean that the Center Director doesn't have confidence in her or his own staff—so what does that mean for the next review? And second, if the Center Director made a mistake in overruling, what confidence can anybody have that other decisions are objective and science-based? And this further raises the question of whether there is a level and predictable playing field for all of regulated industry. Another key problem that comes up when an Office is overruled is in transparency—usually the reasons given for overruling are perfunctory and incorporate conclusory judgments—without making it feasible to objectively evaluate the basis for the decision.

Scientific organizations like FDA work best when a highly trained team reaches consensus on the correct course of action. When an individual has the power to overrule the team, this places the judgment of an individual (who may be influenced by various factors including outside forces) over the scientific judgment of the entire team. While scientific disagreements can be addressed through an appeals process, individual scientists take on senior leaders only at great risk to their own careers—sharply muting the frequency of such appeals. Moreover, there is a tendency in such appeals to provide great deference to the overruling official, precisely because they are a senior leader, reducing confidence of the rank and file that such an appeal would yield any useful outcome.

Of course, if regulatory decisions are made at an even higher level, the cost to trust is commensurately greater. And when there is a perception that regulatory decisions are

influenced by politics, this is most damaging to trust in the objectivity of public health agency recommendations.

Trust is not the only casualty of these interventions—they also make it harder for FDA to retain its most valuable asset—the highly trained and highly motivated people who do the actual work.

It would be unrealistic to assume that politicians would have no interest in vaccine policy in the middle of a pandemic. Of course, they might hope to influence decision making in a way that might increase their political capital. But every time this happens, there is collateral damage to trust. Now if politicians were to own their decisions and state that they were responsible for them, that would at least be transparent and wouldn't affect the trust in the public health Agencies. But if politically appointed and Senate-confirmed Agency heads announce these decisions as though they were the result of the normal processes, it becomes almost impossible for the public or for physicians to figure out which decisions are public health based and which are politically motivated.

Regulatory decision-making during the COVID pandemic

To understand regulatory decision-making about vaccines during COVID, it is important to understand the difference between an Emergency Use Authorization (EUA) and product licensure (or Approval of a Biologics License Application (BLA)). When we refer to an EUA, we typically refer to "Authorization", but when we refer to product licensure, we typically refer to an "Approval".

The statutory standards for EUA and BLA are very different. To issue an EUA FDA must make several determinations[5] including "that, based on the totality of scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: … the product may be effective in diagnosing, treating, or preventing …such disease or condition" and that "the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product…".

Relative to BLA licensure, FDA points out[6]: [t]he "may be effective" standard for EUAs provides for a lower level of evidence than the "effectiveness" standard that FDA uses for product approvals.

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[5] https://www.federalregister.gov/documents/2022/08/29/2022-18527/authorization-of-emergency-use-of-a-biological-product-during-the-covid-19-pandemic-availability

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities

In addition, approval of a vaccine generally requires a more substantial safety database, as well as more robust information about how the product is manufactured and tested, including the requirement that the product be manufactured in approved and inspected facilities.

Criteria for Emergency Use Authorization and Licensure of COVID Vaccines

In the case of COVID, FDA began early discussions about what it would take to license or authorize a COVID vaccine. OVRR wrote two guidance documents—first, one for development and licensure of vaccines[7] (released June 2020) and a follow-up written in August-September 2020[8], once it became clear that vaccines would likely initially be made available via EUA. A vaccine needed to show at least 50% efficacy in clinical trials with 95% statistical confidence that the efficacy was at least 30%. Without foreknowledge of how effective COVID vaccines might be, this set a reasonable target for vaccine efficacy that assured that ineffective vaccines would not be approved—a situation that could be disastrous in a pandemic if it interfered with evaluation of effective vaccines. These criteria also assured that studies would be large enough to obtain a robust safety database. For licensure, safety monitoring of at least 6 months would be expected, while for EUA, total follow-up of a median of 2 months (meaning that half of participants would be followed for at least 2 months) would suffice. This would assure rapid availability of COVID vaccines desperately needed in the growing pandemic while also collecting the minimal safety and efficacy information needed to provide confidence in the vaccine's evaluation[9]. Both of these guidance documents reflected discussions that FDA already had with developers and described agreements regarding criteria for evaluating the ongoing clinical trials. The White House objected to release of the EUA Guidance document and ultimately delayed its release until October 20[10]. At its October 22, 2020 public meeting, the VRBPAC endorsed the criteria as laid out in the EUA Guidance[11].

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[7] https://web.archive.org/web/20200630210553/https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

[8] https://web.archive.org/web/20201201021808/https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19

[9] https://www.nejm.org/doi/full/10.1056/NEJMp2031373, published 10 October 2020

[10] https://www.nytimes.com/2020/10/05/us/politics/coronavirus-vaccine-guidelines.html

[11] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-22-2020-meeting-announcement#event-materials

Licensure of Comirnaty

Pfizer completed its submission of the license application for Comirnaty (its Covid vaccine) on 5/16/21. According to FDA's timelines for priority review, this meant that a decision regarding filing of the application would need to be made by July 16, and a final decision on the application would be reached by 1/16/22.

Because of the high profile of the product, and because OVRR already had substantial experience with the Pfizer vaccine as a result of the EUA review, the team planned to complete its review well before the mandated action due date (ADD). Dr. Gruber and I discussed the feasibility of accomplishing the review more rapidly, and in initial discussions with Dr. Marks in June an agreement was reached that the internal target ADD would be mid-October. The internal target ADD represented OVRR's best estimate of how long it would take to complete the review, and was chosen to be achievable under a range of scenarios. Dr. Marks then came back to Dr. Gruber in early July and requested an earlier internal target ADD. After careful consideration of this request and obtaining feedback from components of OVRR that were responsible for the review (which was already ongoing), as well as other Offices that were contributing to the review (including the Office of Compliance and Biologics Quality and the Office of Biostatistics and Epidemiology), we concluded that it could be possible to promise completion of the review by September 15 (literally less than one third of the 6 months post-filing review time allocated for a priority review, the timeline that is mandated for FDA's highest priority products). This information was conveyed to Dr. Marks in early July, and he initially agreed that this was reasonable. He then followed up on July 8[12] with a request for more information about the proposed timeline for this review. In a July 15 e-mail and attachment[13], Dr. Gruber provided a more detailed explanation of the issues that needed to be addressed in order to complete the BLA review, and pointed out that any timeline depended on responses from Pfizer that were outside of CBER's control. These included review of the substantial quantity of additional data included in the BLA as compared with the original EUA and assessment of the emerging myocarditis signal among recipients of mRNA vaccines.

In a July 16 e-mail[14], Dr. Gruber provided a more granular timeline of activities that needed to take place before approval. This email also pointed out that even a September 15 review ADD would not allow for internal CBER testing of vaccines—which is not a requirement but is often performed at CBER before licensure of novel vaccines. Dr. Gruber also noted that CNN had

[12] https://www.fda.gov/media/168263/download, page FDA-OC-2021-5574-000353
[13] https://www.fda.gov/media/168263/download, FDA-OC-2021-5574-000346-350
[14] https://www.fda.gov/media/168263/download, FDA-OC-2021-5574-000345-357

essentially publicized the internal FDA ADD based on a comment from an unidentified FDA official[15].

However, by then, the Center Director and acting Commissioner had already decided to change course. In a 7/16 10:42 a.m. e-mail[16] to Deirdre Hussey (Director of CBER's Office of Management), Dr. Marks documented his dissatisfaction with Dr. Gruber's assessment of the situation and a 7/16 11:20 a.m. e-mail between Dr. Marks and Dr. Woodcock[17] alluded to the plan for Dr. Marks to take over responsibility for this review from OVRR leadership. It seems clear based on emails on 7/16 and 7/17 between Dr. Marks and Dr. Woodcock that the September 15 internal ADD was considered unacceptable, and Dr. Marks indicated that he had ideas of how to shave time off of the review, but he did not convey those ideas to OVRR.

Sometime between early July and July 16, something had happened to completely change the opinion of Drs. Marks and Woodcock regarding the urgency of completing the BLA review. And it was so important to them that they did not trust the experts who led the Office of Vaccines to do it, even with their help.

In a 7/19/21 meeting memorialized in a 7/21/21 memo by Dr. Gruber, Drs. Woodcock and Marks relieved Dr. Gruber and me of responsibility for managing the ongoing BLA review and placed Dr. Marks in charge. In this meeting, Drs Woodcock and Marks expressed concern about the rising number of COVID cases in the US and globally, largely caused by the Delta variant and stated their opinion that, absent a license, states cannot require mandatory vaccination and that people hesitant to get an EUA authorized vaccine would be more inclined to get immunized if the product were licensed.

While Dr. Gruber was out of town for part of the review period, she and I continued to contribute to the review effort, even as Dr. Marks was leading it. Dr. Marks did not provide a revised internal ADD to the staff, but stated that the goal was to complete the review as rapidly as possible. The Comirnaty BLA was licensed on August 23, 2021.

As predicted by Drs. Woodcock and Marks, vaccine mandates followed immediately afterwards and were announced the same day for DoD and for New York State[18].

If public confidence in a licensed vs. an authorized vaccine was the major concern, FDA would have convened an advisory committee meeting to help provide that assurance to the public.

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[15] https://www.cnn.com/us/live-news/coronavirus-pandemic-vaccine-updates-07-16-21/index.html, posted at 1:42 pm

[16] https://www.fda.gov/media/168263/download, FDA-OC-2021-5574-000351

[17] https://www.fda.gov/media/168263/download FDA-OC-2021-5574-000335

[18] https://www.nytimes.com/2021/08/23/us/pfizer-vaccine-mandates.html

While an advisory committee meeting was not feasible based on the highly accelerated timeframe ultimately employed by FDA for review, and may not have been thought feasible even with the proposed September 15 internal ADD (though the completion of all review activities by August 23 may have actually made this feasible), it certainly would have been feasible based on the originally proposed mid-October timeline. In addition, if public confidence in a licensed vs. an authorized vaccine was considered critical, FDA would have published the Summary Basis for Regulatory Action (SBRA), which provides a summary of FDA's entire review, as soon as possible after the August 23 approval, rather than waiting two and a half months until November 8 to make it available[19].

The rapid move to mandates, which was foreshadowed by other Biden Administration comments[20], suggested that the rapid review of the vaccine was motivated more by a desire to mandate vaccine than by other public health considerations. In this regard, as I explained above, mandates are completely outside of the purview of FDA. Thus, the citation by Dr. Marks and Woodcock of mandates as an important reason for speeding the review strongly implies that pressure to complete the review more rapidly than Dr. Marks originally agreed to be reasonable came from outside of the FDA. And regardless of intent, it seemed clear that the inescapable connection between the vaccine approval and the instantaneous imposition of mandates caused at least some in the public to wonder if the review was as thorough as expected for a license application of this importance.

Booster controversy

Even as the vaccine approval was underway, it became important to understand how well vaccines were performing, especially in the face of new variants. As part of my responsibilities as a liaison to WHO (and as Chair of WHO's Covid Vaccine Expert Working Group), I chaired an international meeting to discuss the potential need for boosters on August 13, 2021[21].

Despite White house briefing data indicating no waning of protection in fully vaccinated individuals against severe disease with any variant[22] President Biden on 8/18 announced that boosters would be made available for everybody over age 16 by September 20 [23]and public

[19] https://www.fda.gov/media/151733/download?attachment
[20] e.g., https://www.nytimes.com/2021/07/01/us/politics/military-va-vaccines.html
[21] https://www.who.int/news-room/events/detail/2021/08/13/default-calendar/who-consultation-on-covid-19-vaccines-research-13-august-2021
[22] https://www.whitehouse.gov/wp-content/uploads/2021/08/COVID-Press-Briefing_18Aug2021-v1.pdf
[23] https://www.washingtonpost.com/health/2021/08/20/biden-coronavirus-booster-shots-criticism/?itid=lk_inline_manual_19

health officials, including Drs. Fauci, Wallensky, and Woodcock said the same thing[24]. While the announcements said that boosting would be subject to FDA and CDC review, setting a one-month deadline for an application that hasn't been received and for which data seemed very equivocal created the impression of pressure to achieve a certain outcome. Moreover, Dr. Woodcock was among those making the announcement, and she and Dr. Marks had already made it clear what would happen if anybody disagreed with her.

Soon afterwards, both Moderna and Pfizer submitted data to support booster doses. After we both submitted our resignations (Dr. Gruber on 8/27, and I on 8/30), Dr. Gruber and I spearheaded work on the briefing document that summarized the available data on the Pfizer vaccine. In the interim, I drafted (and Dr. Gruber co-authored, along with 16 other multidisciplinary vaccine experts from around the world who had participated in the WHO consultation earlier in August) an article published in the Lancet[25] on 9/13, that summarized 93 studies that reported relevant data from around the world, indicating that vaccine protection against severe disease was not waning, even as new variants including the delta variant appeared. The article concluded that boosters were not at that time needed for everybody, but that some people might benefit from boosters, potentially including the elderly and immunocompromised. The article also raised concern that boosters could reduce confidence in the effective two-shot primary regimen and that doses that could be used as boosters would save more lives if given as primary vaccinations. After publication of this article, Dr. Marks removed Dr. Gruber from responsibility for managing the September 17 VRBPAC meeting.

The VRBPAC met on September 17 to discuss the Pfizer booster. Dr. Marks had taken over management of the meeting, and he invited researchers from Israel to present data supporting boosters. This was rather unusual, since the data had not been provided to the committee in advance for review and OVRR did not have the opportunity to review the data. However, some of the preliminary Israeli data were considered in the Lancet article mentioned above, and significant concern for bias and spurious fundings was raised. Of interest, these data were subsequently demonstrated to be confounded due to "heathy vaccinee bias"[26], which means that people who received COVID boosters in this study were much healthier than those who didn't, falsely making it appear that the boosters had helped them.

[24] https://archive.cdc.gov/#/details?url=https://www.cdc.gov/media/releases/2021/s0818-covid-19-booster-shots.html
[25] https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902046-8
[26] https://www.nejm.org/doi/full/10.1056/NEJMc2306683

Despite the Israeli presentation, the committee voted 16-2[27] that the safety and effectiveness data from clinical trial C4591001 did not support approval of a COMIRNATY booster dose administered at least 6 months after completion of the primary series for use in individuals 16 years of age and older. The committee voted unanimously that the known and potential benefits outweigh the known and potential risks of a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine for individuals 65 years of age and older. Following the vote, the committee expressed support that the EUA include individuals at high risk of occupational exposure to COVID-19.

On September 24, FDA issued its emergency use authorization of boosters for individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19[28]. This in essence rejected the original proposal that vaccinees be made available by 9/20/21 to all over age 16 (at least 8 months after the second dose).

Although the FDA ultimately followed the science in its initial booster authorization, the circumstances raised concern among the public that political interference was driving the push for boosters. And ultimately, boosters became mandated for many US college students[29], regardless of prior immunity.

Hydroxychloroquine and Chloroquine EUA

While I was not involved with the hydroxychloroquine and chloroquine EUA, I point out that this was another episode that reduced the credibility of the FDA. In this case, antimalarials in the BARDA stockpile received an EUA for hospitalized COVID patients without other alternatives. The existence of this EUA encouraged people to seek out hydroxychloroquine to treat COVID even in other situations.

Tellingly, the hydroxychloroquine authorization on March 28,2020[30] asserted that the product met the EUA standard (that it was reasonable to believe it may be effective and that known and potential benefits exceeded the risks), but the authorization itself (and the associated fact

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[27] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-17-2021-meeting-announcement

[28] https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations

[29] https://www.washingtonpost.com/outlook/2022/02/10/infection-vaccination-protection-mandates-cdc/

[30] https://web.archive.org/web/20200402050110/https://www.fda.gov/media/136534/download

sheets) cited no data that the FDA reviewed in order to reach this conclusion. My efforts to find a copy of the FDA review in support of this EUA online using internet archives have not been successful.

There was never any evidence credible to an experienced regulator to support effectiveness of hydroxychloroquine in COVID (a finding confirmed in a large randomized study[31]. Given the known risks of hydroxychloroquine and chloroquine, it was essential that there be evidence favoring efficacy in order to support the required determination that the known and potential benefits exceeded the risks[32]. The EUA was withdrawn on June 15,2020 at the request of BARDA based on safety concerns.

If this EUA was appropriate, FDA should have been able to cite a review performed by a qualified review team to support it in the authorizing documents (as indeed, we saw in the EUA authorizations for COVID vaccines[33].

There was strong evidence of a political imperative for this EUA, given the White House's advocacy for the drug[34] and the timing of the enabling declaration, which was issued the day before[35] the EUA was authorized.

Convalescent Plasma

The EUA for convalescent plasma also damaged the credibility of the FDA[36]. FDA issued an EUA for convalescent plasma to treat hospitalized COVID patients on the eve of the 2020 Republican convention, under circumstances that at the time suggested there may have been political involvement. NIH leaders believed that more data were needed to meet the criteria for Emergency Use Authorization, and although the EUA was issued on August 23, 2020, convalescent plasma was not included in NIH COVID treatment guidelines.

Various studies have since shown that any benefit (which is at best, modest) of convalescent plasma is restricted to people who receive it very early in the course of illness—i.e., typically

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[31] https://www.nejm.org/doi/10.1056/NEJMoa2022926

[32] https://fivethirtyeight.com/features/trump-wants-to-use-existing-drugs-to-fight-covid-19-heres-why-we-need-to-test-them-first/

[33] https://web.archive.org/web/20201231100801/https://www.fda.gov/media/144412/download

[34] https://www.cnn.com/2020/03/19/politics/trump-fda-anti-viral-treatments-coronavirus/index.html

[35] https://web.archive.org/web/20200410235155/https://www.fda.gov/media/136539/download

[36] https://www.vox.com/2020/8/24/21399007/trump-covid-19-convalescent-plasma-coronavirus-fda-nih-stephen-hahn

non-hospitalized patients. The EUA has since been modified to restrict use of convalescent plasma to immunosuppressed individuals.

Other Center Director Overrides

In multiple instances[37] including one just this past week[38], the CBER Center Director overruled the review team on Elividys, a muscular dystrophy drug. The review team (including the Office Director) concluded that the product did not meet the standard for licensure, based on review of the studies submitted by the developer. This most recent episode has raised additional concern about the credibility of FDA[39]. The Center Director in each case overruled the review team on technical grounds.

In another instance, the CDER center director overruled a review team and advisory committee to approve eteplirsen, a different muscular dystrophy drug made by the same company[40], also on technical grounds. Of importance, this episode revealed the toothlessness of FDA's scientific disagreement policy—where the Commissioner decided to support the Center Director's authority without considering the scientific merits of the case, which was evaluated through FDA's internal processes and the approval was determined by the Acting Chief Scientist not to have been justified based on FDA's standards.

Solutions and Conclusion

The presented episodes exemplify some of the problems that can occur when the perception arises that political considerations are interfering with the regulatory process. Political interference is enabled by the enormous power vested in individual senior civil servants like Center Directors (and political appointees like Commissioners—or those who aspire to become Commissioner like Acting Commissioners), who have the authority to completely overrule the work of the team units normally responsible for the Agency's output. This can undermine confidence in Federal Agencies even when there is no pandemic and no apparent political pressure. While I can speak most directly to how this works at FDA, I have no doubt that this is a general issue within the Administrative State.

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[37] https://www.biopharmadive.com/news/peter-marks-sarepta-duchenne-gene-therapy-fda/653796/

[38] https://www.statnews.com/2024/06/20/sarepta-duchenne-elevidys-fda-approval-peter-marks-overruled-staff/

[39] https://www.biocentury.com/article/652791/fda-s-different-peter-principle-problem-prioritizing-hope-over-data

[40] https://www.forbes.com/sites/matthewherper/2016/09/20/approving-a-muscular-dystrophy-drug-ignites-civil-war-at-the-fda/

The immense power of senior FDA leaders to overrule entire review teams based on scientific instead of policy disagreements, when utilized, has a corrosive effect on the Agency's credibility. Once a product is approved by an overruling official it is almost impossible to change course, regardless of the outcome of any inquiry.

This concentrated power makes these senior leaders targets for political manipulation. To address these issues, there should be a credible and objective way to address major disagreements that arise between leadership and review teams. Past experience has shown that internal strategies do not work. Accordingly, I would suggest that the senior leader should only overrule the technical review team's scientific judgment if a panel of outside experts (perhaps from the relevant advisory committee) supports the senior leader's position—which should not be a difficult standard to meet. An alternative might be for such disagreements to enter FDA's external appeals process (as though the developer had requested an appeal) for adjudication (recognizing that some modifications might need to be made to assure objectivity).

In addition, flexibility in the EUA standard and lack of transparency regarding its application create opportunities for political interference. The EUA standard (essentially, the product "may be" effective and the known & potential benefits outweigh the risks) is too broad to provide the public with a clear understanding of the level of rigor of underlying regulatory review, and may be subject to political manipulation in an emergency—precisely the time when that type of manipulation may be most dangerous.

Indeed, a fairly high standard was applied to the original EUA of the COVID vaccines, but standards for other decisions were much lower. Even when the EUA was authorized, the COVID vaccines had as much or more clinical data supporting efficacy as compared with many other licensed preventive vaccines. The reason that the vaccines could not be licensed initially was that there was not enough safety data to meet the bar for licensure, and more information was needed regarding chemistry, manufacturing, and controls (CMC), including the facilities used to manufacture the product. On the other hand, boosters met a much lower standard for efficacy and thus were appropriately made available under EUA, even though by that time there was more safety information and the CMC package had been approved in the BLA. In other cases, experts at the time questioned whether the EUA for convalescent plasma and hydroxychloroquine even met the EUA standard, much less the licensure standard.

In a pandemic, it is essential for there to be flexibility to allow availability of life-saving products even if they do not meet the standard for licensure. Thus, I believe the EUA standard is appropriate. However, these examples show that the level of rigor associated with meeting the EUA standard may vary greatly from product to product. There needs to be a way that the public and medical providers can understand, in clear language, what an EUA for a given

product actually means with respect to the FDA review. This higher level of transparency would also reduce the temptation towards political influence.

Where FDA uses the EUA mechanism, I believe that it is important to clearly state, in publicly accessible review memoranda, not only the reasons why FDA believes the product meets each of the EUA criteria (along with their formal benefit-risk analysis), but also to provide a detailed explanation of why the specific product does not meet the standard for licensure. This would provide a basis for placing the EUA into context—and allow the public and medical providers to understand not only that there is an EUA—but what this particular EUA means.