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March 21, 2019

The Honorable Alex Azar
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Secretary Azar and Commissioner Gottlieb:

Our combined experience as Food and Drug Administration (FDA) Special Government Employees totals eight years — one of us as a previous member of the FDA's Drug Safety and Risk Management Advisory Committee (SW, 2008-2012), the other as a member and current chair of the FDA's Anesthetic and Analgesic Drug Products Advisory Committee (RB, 2015-2019). The most common focus of our work on these committees has been prescription opioids. After studying and learning during these many years, we have become increasingly concerned about the FDA's too often dangerously deficient oversight of these drugs. The enclosed citizen petition describes what we believe is the only public health-oriented pathway to reverse this trend.

The petition constitutes an urgent request for you, under your existing legal authority, to immediately impose a moratorium on FDA approval of any new or reformulated opioids. Although we acknowledge that there are many other parties who are complicit in the deadly U.S. prescription opioid epidemic, including the pharmaceutical industry itself, wholesale distributors of prescription opioids, and industry-influenced or inadequately educated physicians, it is beyond question that the FDA is also culpable.

According to FDA data, from 2009 to 2015, as the U.S. prescription opioid crisis was rapidly growing, the agency approved a total of 27 new or reformulated opioids.[1] None, as far as any reliable evidence shows, could remotely be described as a breakthrough opioid, with benefits exceeding risks. Other recently FDA-approved opioids discussed in the petition, including Opana

[1] Chai G, Xu J, Osterhout J, et al. New opioid analgesic approvals and outpatient utilization of opioid analgesics in the United States, 1997 through 2015. *Anesthesiology*. 2018;128(5):953-966.

ER, were much more harmful than beneficial. Absent a currently nonexistent effective regulatory framework for opioids that incorporates public health considerations, the FDA cannot be relied upon to approve any more new opioids.

During 2016, the FDA was internally grappling with the disastrous fallout from reformulated Opana ER, an extended-release form of oxymorphone, a potent opioid that is not used at all in most of the world. The reformulated drug had been approved in December 2011 despite internal FDA preapproval evidence showing that because of the reformulation, the drug could more easily be manipulated to increase intravenous abuse. It was still on the market throughout 2016, despite having been strongly associated in 2015 with a large outbreak of HIV and hepatitis C virus caused by intravenous abuse of the drug. The dangerous reformulated Opana ER would not be taken off the market until mid-2017, by which time prescriptions for the drug totaled approximately 2.4 million.[2]

Partly because of this preventable prescription opioid-induced epidemic, but without publicly admitting to any certain FDA culpability, the agency in 2016 asked for advice from the National Academy of Medicine, now part of the National Academies of Science, Engineering and Medicine (the National Academies). The request was "…to help us develop a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse." [3]

In the summer of 2017, the National Academies' report was finished and delivered to the FDA.[4] The major conclusion of the report's authors was that the FDA had failed to adequately "incorporate public health considerations into opioid-related regulatory decisions." The National Academies therefore recommended many specific changes, compatible with the agency's existing statutory authority, to be incorporated into a new FDA framework for opioid regulation that would address the agency's long-standing deficiencies in this process.

Based on the recommendations to be incorporated into the new opioid regulatory framework, the report further advised that the FDA obtain an independent review of all currently approved opioids and that this "process might lead to the removal of some of the opioid formulations or doses currently on the market because it is highly unlikely that all of these products would be judged safe and effective under the new drug approval framework proposed in this chapter should they just now be entering the market."[5]

Some past FDA opioid approvals, according to the National Academies, likely would not meet the standards included in their recommended framework for opioid regulation, a framework that is clearly not yet in place. It is thus inconsistent with the public-health approach advocated by the

[2] Pages 10-21 in enclosed citizen petition for a moratorium on opioid approvals.
[3] Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. *N Engl J Med*. 2016;374(15):1480-1485.
[4] National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.
[5] *Ibid*. pp. 405-409

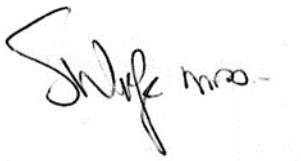
National Academies to continue using the currently inadequate FDA regulatory process for opioid approval and to thereby further endanger public health. The ongoing danger of the deficient FDA regulation of opioids provides a strong case for a moratorium on any future opioid approvals until the National Academies-recommended framework is operational. The experts from the National Academies, drawn from within and outside the practice of medicine, made clear that opioids must be considered as a special drug class requiring substantial modifications of the current regulatory process, as reflected in the following statement:

> "The committee believes that the preceding chapters of this report establish a scientific and epidemiological basis for special treatment of opioids by the FDA that would involve greater integration of public health considerations at the time of preapproval testing, during regulatory review and approval, and during routine post-approval oversight."[6]

Neither Opana ER nor Dsuvia, the newest FDA-approved opioid, would have been approved if such a framework had been in place.

The current opioid crisis is indisputably a national emergency. The FDA must impose a moratorium on approval of opioids until the regulatory framework envisioned by the National Academies is in place.

Sincerely,



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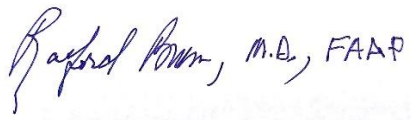

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Enclosure

[6] *Ibid.* p. 361.