Pinney Associates

Science. Strategy. Solutions.

May 10, 2019

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Dear Food and Drug Administration:

These comments are submitted in response to the April 10, 2019 Public Citizen Petition "Requesting an Immediate Moratorium on the Approval of New Drug Applications for New Opioids or New Opioid Formulations".

We write these comments as concerned public citizens with many decades of cumulative experience in addiction, pain medicine, and health policy. As employees of PinneyAssociates, we have extensive experience in advising pharmaceutical companies on the development and assessment of abuse-deterrent (AD) formulations of opioids, *in vitro* and abuse potential assessment, drug scheduling, post-marketing surveillance, and risk management of opioids (including AD formulations) and other drugs that act on the central nervous system.

These comments are our own and do not represent those of any company for which we provide our consulting services. Additionally, these comments were not vetted with anyone outside of our company, nor did any outside organization compensate us for our time to prepare these comments.

First, we commend the Food and Drug Administration (FDA) for the work that has been done to combat the opioid crisis—including efforts to incentivize widespread innovation and development of new treatments for both OUD and pain, including: novel buprenorphine formulations[i], non-opioid medicines, new opioids, and AD formulations of currently existing opioids[ii]. We also believe that the discussion surrounding whether new opioids should be required to demonstrate comparative benefit over the existing armamentarium prior to approval[iii] is extremely important.

A blanket moratorium on all new opioid and new opioid formulation NDAs for any length of time will be detrimental to patient well-being, public health in general, and it would unnecessarily hamper and delay the innovation of safer opioids with less abuse potential. Such an approach means that the millions of people who are and will be best treated by opioids in some form will only have access to those that are currently marketed and not to the safer and lower abuse potential formulations and molecular entities that are beginning to emerge from the pipeline as well as those that might emerge in the future if there is no moratorium.

Given the scope of the opioid epidemic, delaying the approval of medications that could save lives simply because they affect a particular receptor would be a counterproductive and short-sighted strategy based on fear instead of science. The petition requests are well-intentioned; but if applied, they will delay the investment and development of new

products that would be safer with lower abuse potential. At the same time, current opioids with high abuse potential would remain on the market.

The Public Citizen Petition proposal could exacerbate the suffering of pain patients and lead to preventable death

Opioid prescribing has declined, and we agree that overall opioid prescribing needs to decline to a level that provides pain relief to patients without providing excess opioids that can be diverted. Reductions in opioid use are not appropriate for all patients who benefit from opioids. For patients already being treated with opioids, reducing the dose or trying alternatives to opioids should be done with care and sensitivity to the needs of the patient and with careful monitoring during any change in dosing schedule. The worst outcomes for patients result from emerging practices that include seemingly arbitrary reductions in prescribing targets that effectively force providers to deny opioids to patients who are in need, while other prescribers simply choose to stop prescribing opioids altogether. This leads to increased suffering and suicides among chronic pain patients whose pain is not effectively managed[iv], and leads some to turn to illicit opioids[v, vi, vii, viii]. For the approximately 25 million Americans with daily pain and particularly the approximately 10.5 million with considerable daily pain[ix], properly managed opioid treatment can provide meaningful reductions in their pain along with improved function.

For millions of people suffering from moderate to severe pain, currently available non-opioid analgesics do not provide adequate pain relief. And although numerous novel non-opioid targets are being explored within academia and the pharmaceutical industry with the hope that they might work as well as opioids, none are on the imminent horizon to help address the ongoing opioid crisis. Thus, now and for the foreseeable future, opioids will continue to have a critical role in healthcare. Nevertheless, repeated exposure to opioids can cause physical dependence, which can contribute to persistent use; however, this should not be confused with having an OUD as defined in DSM 5. In fact, physical dependence and withdrawal can be readily managed in most opioid maintained patients by tapering their dose according to the drug labeling when opioid therapy is discontinued[x]. Opioids can have other side effects, such as opioid-induced constipation (affecting ~50% of those on chronic opioids) and can cause life-threatening respiratory depression—particularly at high doses, when administered intravenously, and/or in combination with other respiratory depressants. If safer reformulations of current opioids or novel opioids with improved side-effect profiles or reduced abuse potential can be developed (and some are in development now), it would be irresponsible and unethical to delay or halt their development, denying or postponing access to safer pain relievers for the millions of patients who benefit from opioids. Even if potential new opioids are not necessarily safer with respect to potential for abuse or side effects, they may provide a comparative benefit to what is currently available or may fulfill a niche not yet addressed by current opioid alternatives.

The Public Citizen Petition proposal would stifle innovation of better opioids (for pain, OUD, and overdose reversal)

The proposal to enact a sweeping moratorium on opioid approvals does not give weight to the fact that opioids are a diverse class of medications (including agonists, partial

agonists, mixed agonist/antagonists, and antagonists) that have starkly different effects based on their individual unique characteristics. Two formulations of the same opioid can be tremendously different with respect to abuse liability and pharmacologic effects, such as time to peak drug concentration. As the FDA has provided guidance and incentives to approve new, less abuseable medications for pain management, many companies have been working diligently on the development of next-generation opioids such as biased opioid agonists and ever-improving AD formulations.

This quest to improve on opioids by identifying those that would provide pain relief without abuse potential is not new. In 1929, the Committee on Drug Addiction of the National Academy of Sciences was formally tasked with "replacement of all present use of addiction alkaloids by substitutes having no addiction properties," and many in the College on Problems of Drug Dependence (CPDD) still work toward that goal today. With recent advances in molecular science such as the discovery and mapping of biased agonism, we are closer to achieving that goal than ever. This is a critical time for opioid science, and it is crucial that potential manufacturers not be disincentivized to develop these safer opioid alternatives.

Life-saving medications for the treatment of opioid use disorder (i.e., buprenorphine, methadone, and naltrexone) and the reversal of opioid overdose (i.e., naloxone) are all opioids. Long-acting, novel formulations of buprenorphine allow patients to receive prolonged treatment without having to remember to take their medication daily or worry about theft or accidental ingestion by their children. Improvements in sublingual/buccal buprenorphine have also been made recently – such as formulations that dissolve more quickly and lead to better absorption. Given that over 2 million Americans suffer from OUD, it would not make sense to delay innovation in treatment development.

Despite the fact that naloxone is an opioid antagonist, it is still classified as an opioid, and the Public Citizen Petition did not ask that it be excluded from their proposed moratorium. Lower-income populations are perhaps in greatest need of innovation in this area, as naloxone products on the market now are quite costly ($150 – 4,500) and only available by prescription[xi]. There are currently efforts underway to expand access to naloxone by making it available OTC and these efforts have (rightly) received unprecedented support from FDA[xii]. To prevent or unnecessarily delay approval of new naloxone products or other opioid antagonists would be ill-advised as it would bring those efforts to a halt.

Instead of placing undue restrictions on medications for OUD, we need to be expanding access and utilization of these evidence-based treatments. If new formulations make it easier for those with OUD to access and stay in treatment, everything possible should be done to bring those formulations to market, encourage their use, and importantly, ensure that third-party payers are adequately reimbursing these life-saving medications.

The Public Citizen Petition proposal could undermine FDA's efforts to transform the opioid market supply from the most dangerous opioids to safer alternatives

Currently, potential developers have little economic incentive to develop novel AD medications because the existing AD opioids are not being used, in part due to their higher cost relative to non-AD opioids. Some organizations, such as the Veteran's Administration (VA), even have policies against prescribing AD opioids until a patient is

determined to be at high risk for diversion or abuse. These policies have been rationalized by the argument that most patients prescribed opioids do not abuse their medications; and while that is true, diversion from patients to non-patients contributes to a significant portion of abuse of prescription opioids[xiii]. A drastic shift in the prescription opioid supply from easily manipulated and abusable products to safer new analgesics such as AD formulations of opioids will be necessary to fully realize the enormous potential public health benefits that these safer formulations can bring. Although even large-scale replacement of non-AD opioids with their AD counterparts would not solve the opioid epidemic by itself, it is one important component of what will need to be a comprehensive and multi-pronged approach to shift both supply and demand.

In addition to encouraging market transformation toward currently existing AD opioids, we agree with FDA's position that increasing generic access is key to transitioning from a market dominated by existing, less-safe opioids to AD formulations[xiv]. There are currently no generic AD opioids approved, and this poses significant barriers to shifting the market supply in the direction of AD opioids. Generic non-AD opioids are more often abused due to their wider availability and lower cost relative to brand-name alternatives (and, of course, their lack of AD features). Approval of generic AD opioids would reduce the market access barriers imposed by third-party payers and would allow for broader adoption of these safer products. In addition, the high cost of brand name AD opioids places a disproportionate burden on low-income Americans; thus, introducing generic versions could help narrow the current disparity in pain treatment experienced between lower- and higher-income patients.

Significant actions by many healthcare stakeholders, including FDA, prescribers, third-party payers, and possibly legislative bodies will be necessary to encourage and generate meaningful change in the pain medication market.

Our suggestions:

1. Do not enact a blanket moratorium on opioid NDAs

We believe that this would do more harm than good. It will hurt pain patients, patients with OUD receiving medication treatment, and persons who desperately need affordable overdose reversal medication. In addition to the potential immediate harms of prohibiting patients' access to safer medications, this proposal could irreparably reverse industry efforts in the innovation and development of even better opioids, and would still leave more problematic medications on the market.

2. Encourage development, prescription, and reimbursement of AD opioids, including generics, and novel opioids with potentially lower abuse potential and/or respiratory depressant risk.

The FDA has released guidance documents and provided incentives for manufacturers of AD opioids, but we believe that more can and should be done to further this goal. Although not part of FDA's mandate, efforts should be made to the extent possible to ensure adequate reimbursement of these medications as this will be crucial to their widespread use and continued development. Other

federal agencies' (e.g., VA, Medicare, military, etc.) third-party payors should begin to provide support for AD and other safer pain relievers.

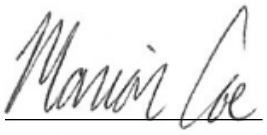
3. Work toward developing a comparative framework for opioid approvals

We agree with the Public Citizen Petition authors and signers that implementation of a regulatory framework for opioid review, approval, and monitoring is necessary to adequately safeguard against the approval of opioids that will likely do more harm than good. This framework might include elements such as more representation of clinicians with direct experience in treating pain and/or OUD on advisory committees and/or a revamping of the Risk Evaluation and Mitigation Strategies (REMS) Programs so the data will be used to develop effective mitigation strategies.

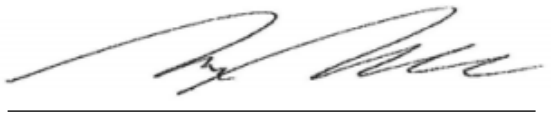
If this proposed moratorium were implemented, all existing opioids, including some of the most problematic, would remain on the market while potentially safer alternatives would be blocked from approval. Incremental advances in pain and addiction medicine are saving lives, and to halt those advancements could lead to suffering and death. The "perfect" opioid may not be discovered soon (or ever), but *better* opioids and formulations have been and continue to be developed. These better opioids are good for patients and good for public health. We urge the FDA not to allow the pursuit of the perfect to become the enemy of the good.

Thank you very much for the opportunity to provide these comments. Please contact Marion Coe at PinneyAssociates at mcoe@pinneyassociates.com or (240) 752-9079 if you have any questions or need further information.

Sincerely,

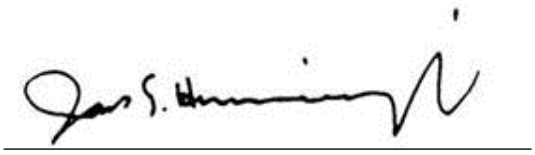


Marion Coe, Ph.D.
Scientist, Population Health Surveillance
PinneyAssociates



Sidney Schnoll, M.D., Ph.D.
Vice President, Pharmaceutical Risk Management Services
PinneyAssociates

Judy Ashworth, M.D.
Chief Medical Officer
PinneyAssociates



Jack E. Henningfield, Ph.D.
Vice President, Research, Health Policy, and Abuse Liability
PinneyAssociates
and
Professor, Adjunct, Behavioral Biology
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine

4800 Montgomery Lane · Suite 400 · Bethesda, MD 20814
(301) 718-8440 · (301) 718-0034 fax

Contributing authors: Rachel C. Beck, Ph.D., August R. Buchhalter, Ph.D., Ed Cone, Ph.D., Karen Gerlach, Ph.D., MPH, Reginald Fant, Ph.D., & John Pinney

REFERENCES

[i] FDA in Brief: FDA finalizes new policy to encourage widespread innovation and development of new buprenorphine treatments for opioid use disorder [news release]. Silver Spring, MD; FDA; February 6, 2019. https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm630847.htm. Accessed April 1, 2019.

[ii] Schnoll SH, Henningfield J FDA Incentivizing Pharma to Develop Less Abusable Pain Medicines. National Pain Report, Alternative Pain Therapy, Government. August 5, 2016. http://nationalpainreport.com/fda-incentivizing-pharma-to-develop-less-abusable-pain-medicines-8831082.html Accessed April 1, 2019.

[iii] Statement by FDA Commissioner Scott Gottlieb, M.D., before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Committee on Appropriations, U.S. Senate. March 28, 2019. https://www.appropriations.senate.gov/imo/media/doc/03.28.19--FY20%20Gottlieb%20Testimony.pdf Accessed April 3, 2019.

[iv] Petrosky E, Harpaz R, Fowler KA, Bohm MK, Helmick CG, Yuan K, Betz CJ. Chronic Pain Among Suicide Decedents, 2003 to 2014: Findings From the National Violent Death Reporting System. Annals of Internal Medicine. 2018 Oct 2;169(7):448-455

[v] Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. New England Journal of Medicine. 2016;374(2):154–163

[vi] Muhuri P, Gfroerer J, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. (August), 2013. [May 25, 2017]. CBHSQ Data Review 2013.

[vii] Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. Annual Review of Public Health. 2015;36:559–574.

[viii] Scholten, W.& Henningfield, J. E. (2016). Response to Kolodny: Negative Outcomes of Unbalanced Opioid Policy Supported by Clinicians, Politicians, and the Media. Journal of Pain & Palliative Care Pharmacotherapy, 30(4), 332-334. doi:10.1080/15360288.2016.1241335

[ix] IOM. (2011). The National Academies Collection: Reports funded by National Institutes of Health. In Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academy of Sciences, Institute of Medicine Committee on Advancing Pain Research.

[x] Volkow ND, McLellan AT. Opioid abuse in chronic pain—Misconceptions and mitigation strategies. New England Journal of Medicine. 2016;374:1253–1263

[xi] Hufford M, Burke DS. The costs of heroin and naloxone: a tragic snapshot of the opioid crisis. STAT. Retrieved from https://www.statnews.com/2018/11/08/costs-heroin-naloxone-tragic-snapshot-opioid-crisis/ Accessed April 23, 2019.

[xii] Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths; Press Announcement, Silver Spring, MD. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629571.htm Accessed April 23, 2019

[xiii] Good, C. B. (2014). VA: Abuse Deterrent Opioid Medication. Paper presented at the Pre-Market Evaluation Of Abuse-Deterrent Properties Of Opioid Drug Products; Public Meeting, Hyattsville, MD. Retrieved from https://www.fda.gov/downloads/Drugs/NewsEvents/UCM590192.pdf Accessed April 3, 2019.

[xiv] Statement from FDA Commissioner Scott Gottlieb, M.D., on steps to promote development of generic versions of opioids formulated to deter abuse [news release]. Silver Spring, MD; FDA; November 21, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm586117.htm Accessed April 3, 2019.