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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use. Docket No. FDA-2022-N-2673

Dear Commissioner Califf:

I am submitting the following comments on behalf of the R Street Institute, a non-profit, non-partisan public policy think tank based in Washington, D.C. The R Street Institute's Integrated Harm Reduction department is committed to promoting harm reduction methods, including those focused on the use of opioids. As the opioid crisis has intensified, naloxone hydrochloride (naloxone) is a critical harm reduction tool for people who use drugs and are at a high risk of overdose.

Although states have made naloxone more accessible through standing orders that allow pharmacists to dispense naloxone without a prescription, allowing over-the-counter (OTC) sales will further improve access to the life-saving drug. The nation needs full market saturation of naloxone to address the scope and severity of the opioid epidemic effectively. Naloxone is remarkably safe and effective and, with the advent of nasally administered and auto-injector administered formulations, easy for the general public to use. For these reasons, we implore the Food and Drug Administration (FDA) to approve naloxone for nonprescription use.

I. Safety of Naloxone Hydrochloride

Approved in 1971 as an injectable product, naloxone has more than 50 years of safety data behind it.¹ Since its introduction as an injectable product, innovations that allow it to be administered nasally and via an auto-injector have been approved for sale in the United States. Auto-injector and nasal naloxone

¹ "Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use; Request for Comments," Food and Drug Administration, Nov. 16, 2022.
<https://www.federalregister.gov/documents/2022/11/16/2022-24874/safety-and-effectiveness-of-certain-naloxone-hydrochloride-drug-products-for-nonprescription-use>.

have been available since 2014 and 2015, respectively.² These innovations made naloxone administration more user-friendly, as they eliminated the need to prepare any equipment before administering the drug.

When used as directed, naloxone presents minimal exposure risks to people experiencing an overdose and to the general public administering the drug. While it is recommended that a person experiencing an overdose receives emergency care after naloxone is administered, this is not due to the action of naloxone itself. Since naloxone is a relatively short-acting drug, it is possible for a person experiencing an overdose to relapse into the overdose after the initial dose of naloxone wears off, which is why emergency care is recommended.³ Those without opioids in their system will not experience any negative effects should they use naloxone.⁴ Allergic reactions to naloxone are also rare.⁵

II. Need for Community Saturation of Naloxone Hydrochloride

Community saturation refers to the idea that there is enough naloxone in a community to ensure that lack of access does not result in overdose death.⁶ Although the exact amount of naloxone needed to reach saturation is difficult to calculate and differs based on the community, most places have not reached community saturation.⁷ One study using data from 2017 found that of the 12 states modeled, only one had sufficient amounts of naloxone in the community to reverse 80 percent of witnessed overdoses—though 100 percent would be considered full community saturation.⁸ The study also found that up to 1,270 additional kits per 100,000 population would be necessary to achieve the 80 percent target in the remaining 11 states.⁹ The authors stress the important role that community-based, no-cost distribution and pharmacy-initiated models play in achieving community saturation.¹⁰ Simultaneously, the study shows there is an acute need for expanded access to naloxone in most places.

Another reason community saturation is important is because the majority of overdoses are reversed by people who use drugs. A study using data from Massachusetts found that 87 percent of overdoses were reversed by people who also used drugs, were engaged in treatment or were in recovery.¹¹ The study also found that most overdose reversal attempts were completed in private settings by friends of the

² Ibid.

³ National Institute on Drug Abuse, “Naloxone DrugFacts,” National Institutes of Health, January 2022. <https://nida.nih.gov/publications/drugfacts/naloxone>.

⁴ Ibid.

⁵ Ibid.

⁶ Alex S. Bennett and Luther Elliott, “Naloxone’s role in the national opioid crisis—past struggles, current efforts, and future opportunities,” *Translational Research* 234 (August 2021), pp. 43-57. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8327685>.

⁷ Michael A. Irvine et al., “Estimating naloxone need in the USA across fentanyl, heroin, and prescription opioid epidemics: a modelling study,” *The Lancet Public Health* 7:3 (March 1, 2022), pp. E210-E218. [https://www.thelancet.com/article/S2468-2667\(21\)00304-2/fulltext](https://www.thelancet.com/article/S2468-2667(21)00304-2/fulltext).

⁸ Ibid.

⁹ Ibid.

¹⁰ Ibid.

¹¹ Alexander Y. Walley et al., “Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis,” *BMJ* 346:f174 (Jan. 31, 2013). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4688551>.

person who overdosed.¹² This is one reason why it is vital to ensure that people who use opioids, as well as people in their immediate network, have access to naloxone.

III. Challenges to Pharmacy-initiated Models

An estimate derived from a sample of 29,382 people living with hepatitis C virus suggests that 80 percent of people live more than 10 miles from a syringe services program (SSP), which often distribute naloxone, and the median distance to an SSP is 37 miles.¹³ By contrast, 90 percent of Americans live within five miles of a pharmacy.¹⁴ As such, pharmacy-based naloxone access—especially if expanded via nonprescription sales—can help eliminate rural-urban access differences.

Evidence shows that pharmacy-initiated models of naloxone distribution increase naloxone prescriptions and decrease opioid overdose deaths.¹⁵ Nevertheless, although pharmacy-initiated models have expanded naloxone access to areas where community-based harm reduction programs do not exist, factors such as stigma, insufficient awareness of naloxone standing orders and limited pharmacy operating hours still serve as barriers to accessing naloxone if it remains behind the pharmacy counter. For example, 44 percent of North Carolina pharmacists surveyed reported dispensing naloxone less than once per month, and a survey of California pharmacists found that only 24 percent were aware that they could dispense naloxone without a prescription.¹⁶ Allowing non-prescription sales of naloxone would prevent pharmacists' unfamiliarity with the intricacies of pharmacy-initiated delivery from being a barrier to sales.

Another factor that can be a barrier to purchasing naloxone from a pharmacist is fear of experiencing stigma. Although there is evidence that medical providers, including pharmacists, sometimes hold stigmatizing beliefs about people with opioid use disorder, the evidence about how this impacts clinical practice related to naloxone distribution is mixed.¹⁷ Regardless of whether individual pharmacists hold

¹² Ibid.

¹³ Lauren Canary et al., "Geographic Disparities in Access to Syringe Services Programs Among Young Persons With Hepatitis C Virus Infection in the United States," *Clinical Infectious Diseases* 65:3 (Aug. 1, 2017), pp. 514-517. <https://academic.oup.com/cid/article/65/3/514/3217637>.

¹⁴ Rachel A. Parry et al., "Pharmacist attitudes and provision of harm reduction services in North Carolina: an exploratory study," *Harm Reduction Journal* 18:70 (July 8, 2021). <https://link.springer.com/article/10.1186/s12954-021-00517-0>.

¹⁵ Paxton Bach and Daniel Hartung, "Leveraging the role of community pharmacists in the prevention, surveillance, and treatment of opioid use disorders," *Addiction Science & Clinical Practice* 14:30 (Sept. 2, 2019). <https://link.springer.com/article/10.1186/s13722-019-0158-0>.

¹⁶ Parry et al., <https://link.springer.com/article/10.1186/s12954-021-00517-0>; Bach and Hartung, <https://link.springer.com/article/10.1186/s13722-019-0158-0>.

¹⁷ Alina Cernasev et al., "'Don't Label Them as Addicts!' Student Pharmacists' Views on the Stigma Associated with Opioid use Disorder," *Innovations in Pharmacy* 12:2 (Jun. 10, 2021). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8326708>; Amy Werremeyer et al., "Pharmacists' stigma toward patients engaged in opioid misuse: When 'social distance' does not mean disease prevention," *Substance Abuse* 42:4 (2021), pp. 919-926. <https://www.tandfonline.com/doi/abs/10.1080/08897077.2021.1900988>; Maryann Z. Skrabal et al., "A Multi-Site Qualitative Study Examining Pharmacy Student Perspectives on the Opioid Crisis," *American Journal of Pharmaceutical Education* 85:7 (Aug. 1, 2021). <https://www.ajpe.org/content/85/7/8515>; Samuel O. Adeosun, "Stigma by Association: To what Extent is the Attitude Toward Naloxone Affected by the

stigmatizing views of people with opioid use disorder, there is evidence that some people who might otherwise seek naloxone from a pharmacist do not do so for fear of experiencing stigma or loss of confidentiality.¹⁸ Nonprescription naloxone would allow people more anonymity in purchasing the drug and might mitigate some of the concerns about experiencing stigma from pharmacy staff. Shifting naloxone to OTC sales reduces the extant high burdens on training and licensure for pharmacy naloxone dispensing.

IV. Opportunities and Challenges of Higher Dose Naloxone Hydrochloride

There is ongoing concern among some harm reduction providers that higher-dose naloxone products—nasal spray greater than 4 milligrams (mg) and naloxone auto-injector greater than 2 mg—may be unnecessary and cause greater discomfort than lower-dose products.¹⁹ Since naloxone can cause a person experiencing an overdose to go into abrupt withdrawal, causing extreme discomfort, higher doses can potentially result in more discomfort without necessarily increasing effectiveness. Nevertheless, some studies have found that the proportion of patients who receive more than one dose of lower-dose naloxone products is increasing, perhaps indicating a need for higher-dose products.²⁰ Additionally, one study of patient perceptions of higher-dose naloxone products found that the majority of patients surveyed either had no preference or preferred higher-dose products compared to lower-dose products if they were personally experiencing an overdose or if they were administering it to another person.²¹ The study also asked community responders about their preference for higher-dose products, and found their preferences were similar to those of the patients.²² Taken together, even accounting for potential discomfort arising from naloxone-precipitated withdrawal, there are few safety concerns related to higher-dose naloxone and there may be a preference among people who use opioids for higher-dose formulations. Since widespread availability of naloxone is vital, it stands to reason that making both dosage formulations accessible is prudent. This will also enable an understanding of use patterns in responding to overdose and provide evidence of increased risk of discomfort from higher doses.

V. No Evidence that Naloxone Hydrochloride Leads to More Drug Use

Stigma regarding nonprescription opioid use is often related to a belief that greater access to naloxone will cause people to perceive opioid use as less risky or encourage people who use opioids to use greater

Stigma of Opioid Use Disorder?”, *Journal of Pharmacy Practice* (May 3, 2022).

<https://journals.sagepub.com/doi/abs/10.1177/08971900221097173>.

¹⁸ Susannah Slocum et al., “If we build it, will they come? Perspectives on pharmacy-based naloxone among family and friends of people who use opioids: a mixed methods study,” *BMC Public Health* 22:735 (April 13, 2022).

<https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-022-13078-z>.

¹⁹ Troy Farah, “How much naloxone is needed to reverse an opioid overdose? New high-dose treatments are raising questions,” *STAT*, Dec. 15, 2021. <https://www.statnews.com/2021/12/15/naloxone-opioid-overdose-zimhi-kloxado>.

²⁰ Ronald B. Moss and Dennis J. Carlo, “Higher doses of naloxone are needed in the synthetic opioid era,” *Substance Abuse Treatment, Prevention, and Policy* 14:6 (Feb. 18, 2019).

<https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-019-0195-4>.

²¹ Ibid.

²² Ibid.

quantities of the substance. Studies have found that among the general public, as well as more vulnerable subpopulations, naloxone access does not decrease the risk perception of heroin use.²³ Similarly, there is no evidence that people who use opioids engage in riskier substance use because of the availability of naloxone.²⁴ Finally, there is also no evidence that overdose frequency increases due to naloxone availability.²⁵

VI. Conclusion

Although the existing pathways for obtaining naloxone have made this life-saving drug more accessible, more can still be done to expand access. Approving naloxone for nonprescription sale is one such tactic. While it is difficult to know how nonprescription naloxone sales will impact naloxone-purchasing cooperatives and community-based distribution groups, it is clear that more needs to be done to reach community saturation. Since cost is one of the primary barriers to naloxone access, it also is important to consider how allowing nonprescription sales will impact insurance coverage and overall cost.²⁶ With major medical organizations, such as the American Medical Association and the American Pharmacists Association, endorsing nonprescription naloxone access, it is clear that medical professionals see a need for expanding access.²⁷ Above all, the FDA should follow the scientific evidence and experience of medical providers and harm reductionists when deciding which, if any, naloxone products are awarded nonprescription status. As the opioid crisis continues to loom, expedient action on the topic of nonprescription naloxone is necessary.

Respectfully submitted,

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²³ Brian C. Kelly and Mike Vuolo, “Do naloxone access laws affect perceived risk of heroin use? Evidence from national US data,” *Addiction* 117:3 (Oct. 6, 2021) pp. 666-676.
<https://onlinelibrary.wiley.com/doi/abs/10.1111/add.15682>.

²⁴ Jermaine D. Jones et al., “No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone,” *Addictive Behaviors* 71 (August 2017), pp. 104-106.
<https://www.sciencedirect.com/science/article/abs/pii/S0306460317301119>; Wai Chung Tse et al., “Does naloxone provision lead to increased substance use? A systematic review to assess if there is evidence of a ‘moral hazard’ associated with naloxone supply,” *International Journal of Drug Policy* 100 (February 2022).
<https://www.sciencedirect.com/science/article/abs/pii/S095539592100431X>.

²⁵ Chung Tse et al. <https://www.sciencedirect.com/science/article/abs/pii/S095539592100431X>.

²⁶ Christina A. Spivey et al., “Evaluation of naloxone access, pricing, and barriers to dispensing in Tennessee retail community pharmacies,” *Journal of the American Pharmacy Association* 60:5 (September – October 2020), pp. 694-701.e1. <https://pubmed.ncbi.nlm.nih.gov/32146134>; Evan D. Peet et al., “Trends in Out-of-Pocket Costs for Naloxone by Drug Brand and Payer in the US, 2010–2018,” *JAMA Health Forum* 3:8e222663.5 (Aug. 19, 2022).
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9391964>.

²⁷ “Increasing Availability of Naloxone H-95.932,” American Medical Association, last accessed June 23, 2022.
<https://policysearch.ama-assn.org/policyfinder/detail/naloxone?uri=%2FAMADoc%2FHOD-95.932.xml>; “Actions of the March 15, 2021 Virtual House of Delegates,” American Pharmacists Association, March 15, 2021.
https://www.pharmacist.com/Portals/0/PDFs/HOD/March_15_2021_Virtual_HOD_Session_Actions_FINAL.pdf?ver=lxbo_r0k5IG0UiHVosA_g%3d%3d.

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