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December 14, 2018

DELIVERED ELECTRONICALLY

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

RE: Docket No. FDA–2018–N–3805; Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments

To the Committee:

The National Health Law Program (NHeLP) appreciates the opportunity to provide comments in response to Federal Register notice FDA-2018-N-3805. NHeLP protects and advances the health rights of low income and underserved individuals by advocating, educating and litigating at the federal and state level.

NHeLP strongly urges the Committee to recommend that the Food and Drug Administration (FDA) immediately initiate a prescription to over the counter (OTC) switch of at least one naloxone product. Naloxone, which has been used for almost fifty years in the clinical setting and over a decade by tens of thousands of laypeople, is, by FDA's own admission, appropriate for OTC marketing. As described in detail below, the FDA Commissioner has the regulatory authority to both initiate and approve a prescription to OTC switch, and in fact is required to move a prescription drug OTC where the prescription requirement is not necessary for the protection of the public health. In the current public health emergency of opioid-related harm, FDA should take all possible measures to increase access to this lifesaving medication, including moving appropriate

naloxone drugs OTC – on the Commissioner’s own motion, if necessary.

I. Background

The United States is experiencing a continuing public health emergency of opioid-related harm.¹ Opioids and opioids in combination with other drugs were responsible for approximately 49,000 deaths in America in 2017, a nearly six-fold increase over the past two decades.² Many of these deaths could have been avoided if persons experiencing opioid overdose had received naloxone, a full opioid antagonist that effectively and quickly reverses most opioid overdoses if administered before the affected individual experiences cardiac arrest.³

Because the probability of irreversible opioid-related harm increases with the amount of time a person remains in opioid-induced respiratory depression, it is imperative that naloxone be immediately available at the scene of the overdose.⁴ This necessarily means equipping people who use drugs (PWUD) as well as their friends and family members with the drug. While community-based organizations and public health entities in many locations distribute naloxone to these individuals, these efforts are currently insufficient to meet the large and growing need for layperson-administered naloxone.⁵

According to Centers for Disease Control and Prevention (CDC) data covering eleven states, bystanders were present at approximately 42% of prescription-only, 44% of illicit-only, and 45% of combined opioid-related deaths in 2016 and 2017, but naloxone was administered in only 0.8%, 4.3%, and 4.4% of cases, respectively.⁶ While the study was not capable of determining why naloxone was not administered, it is likely that in the vast majority of cases it is because it was not readily available. Many of the opioid-

¹ Press Release, U.S. Dept. of Health and Human Services, HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis (October 26, 2017) (on file with author).

² National Center for Health Statistics, *Vital Statistics Rapid Release: Provisional Drug Overdose Death Counts*, <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (last visited Dec. 13, 2018)

³ McClellan, C., Lambdin, B.H., Ali, M., Mutter, R., Davis, C., Wheeler, E., Pemberton, M., Kral, A.H., *Opioid-overdose laws association with opioid use and overdose mortality*, 86 ADDICTIVE BEHAVIORS 90-95 (2018); See also Corey S. Davis & Derek H. Carr, *The Law and Policy of Opioids for Pain Management, Addiction Treatment, and Overdose Reversal*, 14 IND. HEALTH L. REV. 21, 48-49 (“Early reversal of opioid-induced respiratory depression is critical...naloxone, is a pure opioid antagonist that binds to opioid receptors but does not activate them...it displaces those opioids, restoring normal respiratory response”).

⁴ Michiels, C., *Physiological and pathological responses to hypoxia*. 164(6) AMERICAN J. PATHOLOGY 1875-1882 (2004).

⁵ E. Wheeler, et al., *Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014*, 64 MMWR MORB MORTAL WKLY REP 23, 631-35 (2015).

⁶ C. L. Mattson, et al., *Opportunities to Prevent Overdose Deaths Involving Prescription and Illicit Opioids, 11 States, July 2016-June 2017*, 67 MMWR MORB MORTAL WKLY REP 34, 945-51 (2018).

related deaths in those states and others may have been prevented if those bystanders had been equipped with naloxone.

To combat the growing burden of opioid-related harm, every state has moved to increase access to naloxone by modifying statutes and regulations to exempt the drug from many otherwise existing restrictions that apply to prescription medications.⁷ While these changes have increased community access to the medication and contributed to decreases in opioid-related overdose deaths, the fact that naloxone is not immediately present at the scene of many overdoses and the continued increase in opioid-related mortality indicates that they are insufficient and that further regulatory measures are needed.⁸

These state-level changes are attempts to accomplish something only the FDA or Congress can do: make naloxone available without a prescription. Like the legislators in each of the 50 states that have acted to remove some of the barriers to accessing this lifesaving drug, FDA is aware of the pressing need for an OTC naloxone product to reduce opioid-related morbidity and mortality. Indeed, Commissioner Gottlieb recently described OTC naloxone as an “important public health opportunity.”⁹

It is true that FDA has taken unprecedented steps in that direction, including designing a model Drug Facts Label (DFL) and commissioning label comprehension studies.¹⁰ But, as former acting Commissioner Stephen Ostroff, noted, “We cannot stand by while Americans are dying.”¹¹ In the face of the continuing crisis of opioid-related harm, FDA cannot stand by and wait for industry to initiate a prescription-to-OTC switch. FDA should – in fact, must – act to move at least one naloxone product OTC by exercising the authority provided to the Commissioner by controlling regulation.

⁷ C. Davis & D. Carr, *State legal innovations to encourage naloxone dispensing*, 57 J AM PHARM ASSOC S181-84 (2017); C. Davis & D. Carr, *Legal changes to increase access to naloxone for opioid overdose reversal in the United States*, 157 DRUG ALCOHOL DEPEND 112 (2015).

⁸ C. McClellan, et al., *Opioid-overdose laws association with opioid use and overdose mortality*, 86 ADDICT BEHAV (2018); B. H. Lambdin, et al., *Naloxone laws facilitate the establishment of overdose education and naloxone distribution programs in the United States*, 188 DRUG ALCOHOL DEPEND 370 (2018).

⁹ Press Release, U.S. Food and Drug Administration, Statement from FDA Commissioner Scott Gottlieb, M.D., on agency’s efforts to advance new ways to increase the availability of naloxone as one means for reducing opioid overdose deaths (October 23, 2018) (on file with author).

¹⁰ See U.S. Food and Drug Administration, Transcript of Karen Mahoney MD, Deputy Director, Division of Nonprescription Drugs, available at <https://www.fda.gov/Drugs/ScienceResearch/ucm581817.htm> (last visited Dec. 13, 2018) (“The FDA has decided on its own to take an unprecedented step. And so what we have done is on our own we have developed a model drug facts label for a potential over-the-counter Naloxone product”).

¹¹ Press Release, U.S. Food and Drug Administration, FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose (November 18, 2015).

Such a move would not be unprecedented. Indeed, many other countries have recently altered or removed the prescription requirement for this lifesaving drug. In 2016, Australia moved naloxone OTC¹² and Canada removed the drug from its national prescription list, permitting provinces to make the drug available OTC.¹³ Likewise, the United Kingdom has removed many prescription barriers to naloxone.¹⁴ It is time for the FDA to take similar action.

II. The FDA Commissioner has the authority to initiate an OTC switch

Some of FDA's public statements appear to assume that, while naloxone is appropriate for OTC marketing, a switch from prescription-only to OTC status must be initiated by a company that currently markets a prescription-only naloxone product, which must develop an appropriate drug facts label.¹⁵ This is incorrect.

As FDA has publicly acknowledged, the FDA Commissioner has the authority to move a drug from prescription-only to over-the-counter (OTC) status on his own initiative.¹⁶ Indeed, The Commissioner or "any interested person" can initiate the process to exempt a drug from prescription dispensing requirements, and FDA regulations *require* that the Commissioner exempt drugs from prescription requirements when he finds that such requirements are not necessary for the protection of public health and the drugs are safe and effective for use in self-medication "as directed in [the drugs'] proposed labeling."¹⁷ This is the case with naloxone.

¹² S. R. Lenton et al., *Australia Reschedules Naloxone for Opioid Overdose*, 204 MED. J. OF AUSTL. 146, 146-47 (2016).

¹³ Canadian Centre on Substance Abuse, *The Availability of Take-Home Naloxone in Canada*, CCENDU BULLETIN, at 1, 7 (Mar. 2016).

¹⁴ Public Health England, *Guidance: Widening the Availability of Naloxone*, GOV. UK, available at <https://www.gov.uk/government/publications/widening-the-availability-of-naloxone/widening-the-availability-of-naloxone> (last visited Dec. 13 2018).

¹⁵ See *supra* note 9 ("to further encourage companies to enter this space, the FDA created a model DFP and simple pictogram").

¹⁶ M. Kaufman, *FDA Says It Can Take Away Drugs' Prescription Status*, WASHINGTON POST, April 23, 2003 ("The Food and Drug Administration has concluded that it can force drugmakers to switch some of their prescription drugs to over-the-counter medications as a way to make them cheaper and more easily available to consumers").

¹⁷ See 21 CFR § 310.200(b) ("Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(B) of the act may be initiated by the Commissioner or by any interested person").

There are two regulatory pathways available for the Commissioner to initiate a prescription-to-OTC switch: the new drug application (NDA) process, and the monograph process.¹⁸ The NDA pathway may be utilized to move a specific product OTC,¹⁹ whereas the monograph process is utilized to move a drug, class of drugs, or active ingredient OTC when those drugs are generally recognized as safe and effective.²⁰

Option 1: Permit all naloxone drugs to be marketed OTC

FDA has the authority to move a drug, as opposed to a particular product, from prescription to OTC status via the monograph process.²¹ FDA has moved numerous products and classes of products OTC in this manner, including classes of antacids and antiperspirants and, in at least one case, a specific drug.²²

While injectable products are not typically marketed OTC, there is no prohibition on the Commissioner approving an injectable naloxone product for OTC marketing. Indeed, the insulin used by approximately 15% of consumers is available OTC.²³ Additionally, there is a long history of practice evidence showing that people who inject drugs (PWID) are both comfortable with using naloxone for intramuscular injection and that they are capable of doing so.²⁴ While naloxone is not without some risks, it is highly likely to

¹⁸ See generally 21 CFR §§ 314, 330; See also, U.S. Food and Drug Administration, *OTC (Nonprescription) Drugs*.

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ucm209647.html> (last visited Dec. 13, 2018) (“Over-the-counter (OTC) drugs are developed under the OTC Monograph Process or through the New Drug Application (NDA) Process”).

¹⁹ See *id.* (“A sponsor seeking to market its product OTC, either as a new NDA or as a switch from a prescription product, applies to the Division of Nonprescription Drug Products (DNPD) in the Office of Drug Evaluation IV.”).

²⁰ See 21 CFR §§ 330, 330.13; 21 CFR § 310.200(e).

²¹ See W. E. Gilbertson, *The OTC Drug Review – Switch Without Regulation or Application*, 19 Drug Information Journal, 101-109, at 105 (1985) (“Another switch example is a drug not scrutinized by an advisory panel. In October 1982, the FDA proposed a monograph for OTC bronchodilator drug products. Included in this document was the agency’s basic concurrence on the Cough/Cold Panel’s recommendation and the agency’s own decision to classify the drug metaproterenol sulfate in a metered-dose inhalation aerosol as a Category I drug. With that publication, immediate marketing was permitted.” (emphasis added)).

²² K. M. Mahoney, MD, FACE, *Overview of the Over-The-Counter Drug Monograph Process*, June 10, 2016, <https://www.fda.gov/downloads/Drugs/NewsEvents/UCM506382.pdf>.

²³ See Kaiser Health News, *You Can Buy Insulin Without A Prescription, But Should You?*, Dec. 14 2015, <https://khn.org/news/you-can-buy-insulin-without-a-prescription-but-should-you/> (last visited Dec. 13, 2018).

²⁴ Indeed, naloxone for intramuscular injection is by far the most prevalent form distributed by Overdose Education and Naloxone Distribution (OEND) programs that provide naloxone to PWID and their peers. See E. Wheeler, et al., *Opioid Overdose Prevention Programs Providing Naloxone to Laypersons — United States, 2014*, 64 MMWR MORB MORTAL WKLY REP 23 (July 3, 2015).

have a better safety profile than insulin, which can cause severe harm up to and including death if administered at inappropriate doses.²⁵ Additionally, many programs distribute an injectable formulation of naloxone together with a mucosal atomizer device so that the drug can be administered intranasally.

Option 2: Move one or more specific naloxone products to OTC status

Perhaps the more appropriate option, however, is for some naloxone products to remain prescription only while one or more products currently labeled for layperson use (brand names Narcan® and Evzio®) are moved to OTC status.

Federal law requires that drugs be available via prescription where they can be used only “under the supervision of a practitioner licensed by law to administer such drug.”²⁶ By FDA’s own admission, that is not the case with these products. In general, a product is appropriate for OTC marketing where 1) its benefits outweigh its risks; 2) the user can understand when and how to administer the medication without consulting a medical professional; 3) the drug is effective when used as recommended; 4) the drug has a low potential for misuse and abuse; and 5) the drug can be appropriately labeled.²⁷ These two drugs meet all these criteria.

Naloxone is safe and effective.²⁸ Overdose is easily recognizable by laypeople and laypeople can effectively respond with naloxone, even when they have not been specifically trained in either overdose recognition or naloxone administration.²⁹ Naloxone in many formulations has been distributed to laypeople without direct provider

²⁵ K. S. Russell, et al., *Insulin overdose among patients with diabetes: a readily available means of suicide*, 11 PRIM CARE COMPANION J CLIN PSYCHIATRY 258 (2009).

²⁶ 21 USC § 353(b)(1).

²⁷ See generally *supra* note 21; see also U.S. Food and Drug Administration, *Division of Nonprescription Drugs (DNDP)*, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm093452.htm>, (last visited Dec. 13, 2018) (“OTC drugs generally have these characteristics: their benefits outweigh their risks; the potential for misuse and abuse is low; consumer can use them for self-diagnosed conditions; they can be adequately labeled; health practitioners are not needed for the safe and effective use of the product”).

²⁸ See R. R. Lynn and JL Galkin, 9 THER. ADV. DRUG. SAF. 63 *Naloxone dosage for opioid reversal: current evidence and clinical implications* at 80 (2018) (“in the hands of laypeople ... the risk of inadequate reversal of opioid toxicity is far greater than the risk posed by over-antagonizing respiratory depression to the point of precipitating opioid withdrawal, as the latter is unpleasant but rarely life-threatening, while untreated opioid overdose is frequently fatal, particularly as the incidence of overdose due to potent synthetic opioids rises.”); See also Nat’l Institute of Health, *Opioid Overdose*, <https://medlineplus.gov/opioidoverdose.html> (last visited Dec. 13, 2018) (“Naloxone is a safe medication that can quickly stop an opioid overdose”).

²⁹ M. Doe-Simkins, et al., *Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study*, 14 BMC PUBLIC HEALTH (2014).

consultation for over a decade, with tens of thousands of successful reversals reported.³⁰ Indeed, as the Surgeon General has noted, “in most states, you can walk into a pharmacy and request naloxone even if you don’t already have a prescription.”³¹ The potential for misuse or abuse of naloxone, which is not a controlled substance and has no euphoric effect, is extremely low.³²

In the case of Narcan® and Evzio®, current labeling meets guidance on consumer-friendly DFLs: the labels list the product’s active ingredient, dosage information, the purpose of the product, uses for the product, specific warnings, and an inactive ingredient list.³³ Indeed, FDA has noted that Narcan in its current formulation “can be used on adults or children and is easily administered by anyone, even those without medical training” and that Evzio “can be used by family members or caregivers to treat a person known or suspected to have had an opioid overdose.”³⁴ To the extent that any additional label changes are deemed necessary, FDA can and should quickly adapt the model DFL it has created to meet the specific requirements of each product to be moved OTC.³⁵

³⁰ The signs and symptoms of opioid overdose are easily recognizable and laypeople are best situated to intervene. See generally Nat’l Institute of Health, *Opioid Overdose*, <https://medlineplus.gov/opioidoverdose.html> (last visited Dec. 13, 2018), Daniel Kim, et al, *Expanded Access to Naloxone: Options for Critical Response to the Epidemic of Opioid Overdose Mortality*, 99 HEALTH POLICY AND ETHICS 3 (Mar. 2009) at 402 (“The peers or family members of overdose victims, however, are most often the actual first responders and are best positioned to intervene”), E. Wheeler, et al., *Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014*, 64 MMWR MORB MORTAL WKLY REP 23, 631-35 (2015).

³¹ Press Release, U.S. Dept. of Health and Human Services, Surgeon General Releases Advisory on Naloxone, an Opioid Overdose-Reversing Drug (April 5, 2018) (on file with author).

³² Naloxone is not a controlled substance and has little to no potential for abuse. See U.S. Drug Enforcement Agency, *Controlled Substances*, https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf.

³³ See 21 CFR § 201.66.

³⁴ See Press Release, U.S. Food and Drug Administration, FDA approves new hand-held auto-injector to reverse opioid overdose, (Apr. 3, 2014) (on file with author) (“The [FDA] today approved a prescription treatment that can be used by family members or caregivers to treat a person known or suspected to have had an opioid overdose...”); See also Press Release, U.S. Food and Drug Administration, FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose (November 18, 2015) (on file with author) (“[Narcan] can be used on adults or children and is easily administered by anyone, even those without medical training”).

³⁵ 21 CFR § 330.10(a)(4)(v) (“Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.”); U.S. Food and Drug Administration, Transcript of Karen Mahoney MD, Deputy Director, Division of Nonprescription Drugs, available at <https://www.fda.gov/Drugs/ScienceResearch/ucm581817.htm> (last visited Dec. 13, 2018)

There is no requirement in statute or regulation that any labeling changes be undertaken by a manufacturer; indeed, the FDA has already created model OTC labels and it is clear that the Commissioner can move an appropriately labeled product OTC on her own authority.³⁶

The Commissioner should move expeditiously to initiate an Rx-to-OTC switch

The Department of Health and Human Services, acting at the direction of President Trump, has declared opioid-related morbidity and mortality a public health emergency.³⁷ FDA has made clear that naloxone is a key component of our nation's response to this epidemic, and extensive evidence suggests that increased access to it will reduce opioid-related harm in the United States. The Surgeon General has noted that "increasing the availability and targeted distribution of naloxone is a critical component of our efforts to reduce opioid-related overdose deaths and, when combined with the availability of effective treatment, to ending the opioid epidemic."³⁸ The drug's prescription-only status is not necessary for the protection of public health and in fact acts as an impediment to naloxone access, particularly distribution through health departments, community-based organizations, and other venues that serve many of the people at highest risk of opioid overdose.

While increased access to injectable naloxone might have the greatest effect on the epidemic because those generic formulations are less expensive than the branded products and therefore most often distributed by programs that provide naloxone directly to PWUD, practicality may militate in favor of having both prescription-only and OTC naloxone products available simultaneously.³⁹ We therefore suggest that the Committee recommend that the Commissioner immediately initiate the process to move one of the branded products (Evzio and Narcan) to OTC status, and study the merits of pursuing a monograph change for the active ingredient while urging Congress and the

("The FDA has decided on its own to take an unprecedented step. And so what we have done is on our own we have developed a model drug facts label for a potential over-the-counter Naloxone product").

³⁶ See *supra* note 16.

³⁷ See *supra* note 1.

³⁸ U.S. Dept. of Health and Human Services, Surgeon General's Advisory on Naloxone and Opioid Overdose, <https://www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html> (last visited Dec. 13, 2018).

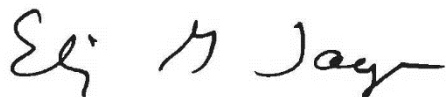
³⁹ While the Affordable Care Act mandates that many health insurers to cover naloxone under the Essential Health Benefits requirement, that mandate applies only to prescription drugs. Both Congress and state governments can and should act to require insurance coverage of naloxone, whether prescription-only or OTC. See Centers for Medicare and Medicaid Services (CMS) Center for Consumer Information and Insurance Oversight, *Essential Health Benefits Bulletin* (Dec. 16, 2011), https://www.cms.gov/CCIIO/Resources/Files/Downloads/essential_health_benefits_bulletin.pdf.

Department of Health and Human Services to require public and private insurance coverage of all forms of naloxone.

Although FDA typically relies on NDA holders to initiate an OTC switch, it is clear that no current holders are interested in initiating that process. It is also clear that, while this practice is customary, it is not required by statute or regulation. FDA itself recognizes that the agency has the authority to force an OTC switch even without action by the NDA holder. FDA enjoys great leeway in its drug approval processes, even when acting in new, different, or innovative ways, so long as it can articulate a cogent rationale for its actions.⁴⁰ If there was ever a time to put that ability to use, now is that time. Thousands of lives may depend on FDA taking bold action to increase access to this life-saving medication.

If you have any questions regarding these comments, please contact NHeLP Senior Attorney Corey Davis at (310) 736-1657 or davis@healthlaw.org.

Sincerely,



Elizabeth G. Taylor
Executive Director

⁴⁰ See *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 27 (D.D.C. 1996) (holding that the FDA did not act unlawfully when it approved a drug for use by patients with multiple sclerosis without requiring clinical trials for the drug); See also L. Noah, *Treat Yourself: Is Self-Medication the Prescription for What Ails American Health Care?* 19 HARVARD J. L. AND TECH. 360 (Spring 2006) at 384 (“Although the FDA enjoys largely unreviewable discretion in exercising its enforcement powers, courts have chastised the agency...If, however, the FDA can offer a cogent explanation for taking a novel approach to a regulatory issue, then courts will defer to its expertise.”).