INCREASING ACCESS TO NALOXONE: OVERCOMING SOCIETAL CHALLENGES TO REDUCE OPIOID OVERDOSE FATALITIES

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I. INTRODUCTION

Over the past several years, there has been increasing interest and research focused on understanding and mitigating both acute and chronic pain.[1,2] These interests, and research endeavors, include measures to both encourage the safe use and deter the abuse of opioid analgesics commonly prescribed for moderate-to-severe chronic pain. In an effort to reduce the risks associated with opioids, the United States Food and Drug Administration (FDA) has approved a risk management plan, the Risk Evaluation and Mitigation Strategy (REMS) for extended release (ER) and long-acting opioid analgesics to ensure health care providers are properly trained on how to prescribe these medications.[3]

In addition to focusing on physicians properly prescribing opioids, the FDA REMS focuses on the safe use of opioids by patients in an effort to prevent abuse and potential overdose.[4] Over the past decade, rates of fatal drug overdose have more than doubled in the United States, becoming one of the leading causes of preventable injury death.[5] Although fatal drug overdose can be attributed to the use and abuse of illegal narcotics, abuse of prescription drugs has increased over the years and is a contributing factor to drug overdose fatalities.[6,7] Prescription drug abuse is not only a growing public health concern in the

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[1] *See* DEP'T OF DEF., *Program Announcement for the Def. Health Program Defense Medical Research and Development Program* (2013) http://cdmrp.army.mil/funding/pa/13dmrdpcrmrpnsra_pa.pdf (seeking research applications addressing alternatives to current opioid analgesics for severe pain management and strategies for the management of acute and chronic pain).

[2] W.M. Compton et al., *Expanding Access to Opioid Overdose Intervention: Research, Practice, and Policy Needs*. 158 Annals of Internal Med. 65, 65–66 (2013) [hereinafter Compton].

[3] *See* U.S. FOOD & DRUG ADMIN, *FDA Works to Reduce Risk of Opioid Pain*, http://www.fda.gov/forconsumers/consumerupdates/ucm307821.htm (last updated Nov. 25, 2013) (describing the FDA REMS).

[4] *Id.*

[5] *See* Compton, *supra* note 2, at 65.

[6] *See* CTRS. FOR DISEASE CONTROL & PREVENTION, PRESCRIPTION DRUG ABUSE AND OVERDOSE: PUBLIC HEALTH PERSPECTIVE. (Oct. 24, 2012), http://www.cdc.gov/primarycare/materials/opoidabuse/docs/pda-phperspective-508.pdf (including a line graph displaying an increasing death rate from 1999–2010).

[7] CTRS. FOR DISEASE CONTROL & PREVENTION, VITAL SIGNS: OVERDOSES OF PRESCRIPTION OPIOID PAIN RELIEVERS – UNITED STATES, 1999 – 2008, 60 Morbidity and Mortality Weekly Rep.1487-92 (Nov. 4, 2011), http://stacks.cdc.gov/view/cdc/29055 [hereinafter CDC VITAL SIGNS].

United States but impacts other countries as well. As reported by the International Narcotics Control Board, globally, more people abuse prescription drugs than heroin, cocaine, and ecstasy combined.[8]

In response to the growing number of overdose related fatalities, several states,[9] including Maryland[10] have implemented opioid overdose response programs. The purpose of these programs is to help prevent and/or reduce the number of opioid overdose fatalities when emergency medical services (EMS) are not immediately available. To prevent opioid overdose, these programs teach non-medical personnel how to recognize an overdose and provide care to an individual experiencing an overdose, which includes administration of the opioid antagonist naloxone.[11,12]

The enactment of statewide opioid overdose response programs presents several unique legal questions including physician, nurse practitioner, and/or third-party administrator liability related to prescribing and dispensing naloxone (a prescription drug) and the unlicensed practice of medicine. In addition to the legal concerns associated with increasing access to naloxone, there are also public health concerns associated with these programs. These concerns include: (1) the safety of naloxone administration by unlicensed persons and a lack of follow-up care for overdose victims; (2) the facilitation of drug misuse and abuse by acting as a safety-net to opioid users; and (3) the costs associated with executing the programs.

Although the legal and public health concerns associated with statewide opioid overdose response programs have been addressed by legislation and empirical data, regulatory action by

[8] *See generally* INT'L NARCOTICS CONTROL BD., REP. OF THE INT'L NARCOTICS CONTROL BOARD FOR 2011, U.N. SALES NO. E.12.XI.5 (2012) http://www.unodc.org/documents/southasia/reports/2011_INCB_ANNUAL_REPORT_english_PDF.pdf (last visited Sept. 24, 2015) (providing an analysis on global drug activity for 2011).

[9] *See* NETWORK FOR PUB. HEALTH LAW, LEGAL INTERVENTIONS TO REDUCE OVERDOSE MORTALITY: NALOXONE ACCESS AND OVERDOSE GOOD SAMARITAN LAWS (2015), https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf (last visited Sept. 24, 2015) [hereinafter STATE PROGRAMS] (providing a list of state-based opioid overdose response programs).

[10] MD. CODE ANN., HEALTH GEN. §§ 13-3101–3111 (West 2013) *amended by* 2015 Md. Laws 356.

[11] *Id.* at § 13-3108.

[12] *See* STATE PROGRAMS, *supra* note 9.

the FDA may obviate the need for these programs or, at the very least, supplement program efforts by increasing access to naloxone. To increase access to naloxone, advocates have proposed that the FDA approve a switch in naloxone's prescription status so that it may be marketed as an over-the-counter (OTC) drug and/or approve an intranasal formulation of naloxone for use in non-medical settings.[13]

To address the regulatory requirements associated with expanded access to naloxone, the FDA Center for Drug Evaluation and Research, the Office of the Assistant Secretary for Health, the National Institute on Drug Abuse (NIDA) and the Centers for Disease Control and Prevention hosted a scientific workshop in April 2012.[14] At this meeting, the FDA provided details regarding regulatory pathways for the approval of alternate naloxone formulations and information required to facilitate a switch in the prescription status of naloxone to OTC.[15] The question remains however whether there is sufficient industry interest to conduct the requisite studies and traverse the regulatory landscape in order to increase access to naloxone. Given the lack of industry interest, the most appropriate mechanism to facilitate increased access to naloxone is action by federal agencies supporting the research and development of alternate formulations of the drug and providing guidance to facilitate its regulatory approval.

II. PAIN, ADDICTION & OVERDOSE: THE OPIOID CONUNDRUM

Chronic pain is a significant medical problem in the United States. According to the Institute of Medicine, there are approximately one hundred million persons living with pain in

[13] Scott Burris et al., *Stopping an Invisible Epidemic: Legal Issues in the Provision of Naloxone to Prevent Opioid Overdose*, 1 Drexel L. Rev. 273, 330–40 (2009), http://prescribetoprevent.org/wp-content/uploads/2012/11/burris_stoppinganinvisibleepidemic.pdf [hereinafter Burris] (outlining the challenges of converting Naloxone to an OTC medication and obtaining approval of a nasally administered formula of Naloxone).

[14] *See generally* FDA, ROLE OF NALOXONE IN OPIOID OVERDOSE FATALITY PREVENTION 1, 165–90, http://www.fda.gov/Drugs/NewsEvents/ucm277119.htm (follow "Transcript: Thursday, April 12, 2012") (Apr. 12, 2012) (discussing efforts taken by the federal government to address the problem of prescription overdose deaths, with specific attention to naloxone) [hereinafter FDA MEETING TRANSCRIPT].

[15] *Id.* at 163.

the United States.[16] Thus, nearly one-third of the American adult population experiences chronic pain.[17] Despite nearly one-third of the adult American population experiencing chronic pain, it is often undertreated. Estimates from the American Academy of Pain suggest that greater than 50 percent of patients with moderate-to-severe pain do not get adequate relief from their prescribed analgesics.[18] Further, nearly 29 percent of patients with severe pain change their healthcare provider up to three times per year due to perceptions of suboptimal pain care.[19] In addition, the financial costs associated with pain management range from $560-$635 billion per year.[20]

Chronic pain is primarily treated with opioids. The classification of opioids includes natural,[21] semi-synthetic,[22] and synthetic[23] compounds with morphine-like properties that bind to opioid receptors,[24,25] which are widely distributed in the brain and body.[26] Opioid receptors involved in pain modulation are located in both the central and peripheral nervous systems.[27] These receptors also bind to endogenous opioid peptides (endorphins)

[16] INST. OF MED. OF THE NAT'L ACADS., RELIEVING PAIN IN AMERICA: A BLUEPRINT FOR TRANSFORMING PREVENTION, CARE, EDUCATION, AND RESEARCH (June 29, 2011), http://iom.nationalacademies.org/reports/2011/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care-education-research.aspx (follow "Report Brief: PDF" hyperlink) (last visited Sept. 25, 2015) [hereinafter *IOM Report*].

[17] *Id.*

[18] Roper Starch, *Chronic Pain in America: Roadblocks to Relief*, AM. PAIN SOC'Y, http://www.doctordeluca.com/Library/Pain/ChronicPainRoadblocks.htm (last visited Sept. 24, 2015).

[19] *Id.*

[20] *See IOM Report*, *supra* note 16.

[21] Andrew Rosenblum et al., *Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions*, 16 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 405 (2008), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711509/pdf/nihms 97365.pdf (last visited Sept. 24, 2015) [hereinafter Rosenblum] (stating that natural opioids include those that are derived from the opium poppy such as morphine and codeine).

[22] *See id.* at 3 (explaining that semi-synthetic opioids include drugs that are synthesized from naturally occurring opiates, i.e. heroin from morphine and oxycodone from thebaine).

[23] *See id.* (stating that synthetic opioids include methadone, fentanyl, and propoxyphene).

[24] *Id.*

[25] *See generally* Ream Al-Hasani & Michael R. Bruchas, *Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior*, 115 J. OF AM. SOC'Y OF ANESTHESIOLOGISTS 1363, 1363 (2011) (stating that opioid receptors include mu, kappa, and delta receptors).

[26] *See* Rosenblum, *supra* note 21, at 3.

[27] *Id.*

which are involved in the modulation of pain, reward mechanisms, mood and stress.[28]

In the United States, several opioids have been commercialized for medical use, either alone, or in combination with other pain-relieving medications.[29] These medications can be delivered via oral, transdermal or intravenous routes of administration.[30] When taken as prescribed, opioids can safely and effectively manage pain, however, patients using opioids may experience a "diverse array of side effects."[31] Side effects mediated by peripheral mechanisms include reduced peristalsis,[32] nausea, and itch.[33] Side effects of opioid use mediated by the central nervous system may cause pupillary constriction, somnolence, mental clouding, mood effects (euphoria or dysphoria) and respiratory depression.[34]

Although opioids are the most effective drugs for relieving pain, their use may also be subject to stigmatization[35] as they are also associated with abuse, addiction, and diversion.[36] Despite the abuse liability of opioids, therapeutic opioid production and distribution has increased substantially over the past twenty years.[37] For example, morphine production has increased extensively with 168 tons produced in 1993 and a projected 788 tons produced in 2012.[38] Further, the global production of

[28] *Id.* at 3–4.

[29] *See id.* at 3 (stating that commercialized products include but are not limited to OxyContin®, Vicodin®, Lorset®, Ultracet® and Percocet®).

[30] *See id.* (acknowledging that in an ambulatory setting, oral and transdermal formulations are the favored routes of administration for treating pain).

[31] *Id.*

[32] MedlinePlus, *Peristalsis*, U.S. NAT'L LIBR. OF MED., https://www.nlm.nih.gov/medlineplus/ency/anatomyvideos/000097.htm (last updated Nov. 5, 2012) (explaining that peristalsis occurs when the smooth muscles of the digestive tract contracts to propel contents forward).

[33] *See* Rosenblum, *supra* note 21, at 3, 6.

[34] *Id.* at 3 (citing J.H. Jaffe et al., *Neurology of Opiates/Opioids, in* TEXTBOOK OF SUBSTANCE ABUSE TREATMENT 11 (M. Galanter et al., 2th ed. 1999)).

[35] Bruce G. Link et al., *On Stigma and Its Consequences: Evidence From a Longitudinal Study of Men with Dual Diagnoses of Mental Illness and Substance Abuse*, 38 J. OF HEALTH & SOC. BEHAV. 177, 179 (1997) (defining stigma as a "'mark' that (1) sets a person apart from others, and (2) links the marked person to undesirable characteristics.").

[36] *See* Rosenblum, *supra* note 21, at 3, 4, 6–7.

[37] Laxmaiah Manchikanti et al., *Lessons Learned in the Abuse of Pain-relief Medication: A Focus on Healthcare Costs*, 13 EXPERT REV. NEUROTHERAPEUTICS 527, 527 (2013) [hereinafter *Laxmaiah*].

[38] *Id.* (citing Benedikt Fischer & Elena Argento, *Prescription Opioid Related Misuse, Harms, Diversion and Interventions in Can.: A Rev.*, 15 PAIN PHYSICIAN

oxycodone rose by over 4000 percent from 1993 to 2012.[39] With respect to the sale and distribution of opioids, data demonstrates an increase from 96 mg of morphine equivalents per person in the United States in 1997 to 700 mg per person in 2007.[40,41] The quantities of morphine equivalents sold and distributed in the United States are enough to supply 5 mg of hydrocodone, every 6 hours, for 45 days to every adult American.[42]

The increase in production and sale of opioids over the past twenty years may be partially attributed to state medical boards lessening the restrictions on prescribing opioids for treating chronic, non-cancer pain, following the release of guidelines by the Federation of State Medical Boards (FSMB) of the United States.[43] Data suggests that in the United States the number of opioid prescriptions filled exceeded 256 million in 2009.[44] Of these prescriptions, 234 million were for immediate-release opioids and 22.9 million for ER opioids.[45] Due to the risks associated with opioids, including addiction, overdose, and death, the FSMB has since revised its model policy to "emphasize[] the professional and ethical responsibility of physicians to appropriately assess and manage patients' pain, assess the relative level of risk for misuse and addiction, [and] monitor for

J. ES191, ES192 (2012), http://www.painphysicianjournal.com/ (follow "Past Issues" hyperlink; then follow "Archives: 2012" dropdown list; then follow "July (Vol. 15, Issue. 3S)" hyperlink; then follow "2012;15 ;ES191-ES203" hyperlink) (last visited Sept. 25, 2015)); *See also* INT'L NARCOTICS CONTROL BD., NARCOTIC DRUG TECHNICAL REP. 2011: ESTIMATED WORLD REQUIREMENT FOR 2012 - STATISTICS FOR 2010 (2011), U.N. SALES NO. T.12.XI.2 (2012), http://www.incb.org/ incb/en/narcotic-drugs/Technical_Reports/2011/narcotic-drugs-technical-report_2011.html (follow "PDF" hyperlink) (last visited Sept. 24, 2015).

[39] *See* Laxmaiah, *supra* note 37.

[40] CTRS. FOR DISEASE CONTROL & PREVENTION, CDC GRAND ROUNDS: PRESCRIPTION DRUG OVERDOSES – A U.S. EPIDEMIC, 61 Morbidity and Mortality Weekly Rep. 10–13 (2012), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm (last visited Sept. 24, 2015).

[41] *Id.*

[42] Laxmaiah Manchikanti et al., *Opioid Epidemic in the U.S.*, 15 PAIN PHYSICIAN J. ES9, ES22 (2012), http://www.painphysicianjournal.com/ (follow "Past Issues" hyperlink; then follow "Archives: 2012" dropdown list; then follow "July (Vol. 15, Issue. 3S)" hyperlink; then follow "2012;15;ES9-ES38" hyperlink) (last visited Sept. 25, 2015).

[43] *Id*. at ES10 (citing *Model Policy for the Use of Controlled Substances for the Treatment of Pain,* FED'N OF ST. MED. BDS. OF THE U.S. (May 2004), http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/model04.pdf (last visited Sept. 24, 2015)).

[44] *Id.* at ES23.

[45] *Id.* at ES24.

aberrant behaviors and intervene as appropriate."[46]

Drug abuse and subsequent overdose has become a major public health concern.[47] "In 2008, a total of 36,450 drug overdose deaths (i.e., unintentional, intentional [suicide or homicide] or undetermined intent) were reported, with prescription opioid[s] . . . cocaine, and heroin identified as being the drugs most commonly involved."[48] Of those deaths, a drug was specified in 27,153 (74.5 percent) of cases.[49] A primary risk factor for overdose is the chronic use of opioids, alone, or in combination with other drugs.[50] For example, of the 27,153 drug overdose deaths in the United States in 2008 in which a drug was specified, one or more prescription drugs were involved in 20,044 (73.8 percent) of those overdose deaths.[51] Further, of the 20,044 prescription drug overdose related deaths, opioid pain relievers were involved in 14,800 (73.8 percent) of cases.[52]

In parallel to the national statistics,[53] Maryland has also experienced rising rates of opioid-related deaths in recent years.[54] Further, while the number of heroin-related deaths decreased between 2009 and 2011, the number of prescription opioid-related deaths increased.[55] The number of heroin-related deaths

[46] *Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain,* FED'N OF ST. MED. BDS. OF THE U.S.. 3 (July 2013), http://www.fsmb.org/Media/Default/PDF/FSMB/Advocacy/pain_policy_july2013.pdf (last visited Sept. 24, 2015).

[47] CTRS. FOR DISEASE CONTROL & PREVENTION, COMMUNITY-BASED OPIOID OVERDOSE PREVENTION PROGRAMS PROVIDING NALOXONE U.S., 2010, 61 Morbidity and Mortality Weekly Rep.101–05, (2012), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6106a1.htm [hereinafter *Opioid Overdoes Prevention Programs*].

[48] *Id.*

[49] *See* CDC VITAL SIGNS, *supra* note 7.

[50] MD. DEP'T OF HEALTH AND MENTAL HYGIENE, FACT SHEET, HEROIN OVERDOSE DEATHS ON THE RISE, RX OPIOID OVERDOSE DEATHS DOWN, (Dec. 7, 2012), http://bha.dhmh.maryland.gov/OVERDOSE_PREVENTION/Documents/StatewideOverdoseDeathTrendFactsheetFINAL%20(5).pdf [hereinafter Md. Dep't of Health and Mental Hygiene Fact Sheet].

[51] *See* CDC VITAL SIGNS, *supra* note 7.

[52] *Id.*

[53] Margaret Warner ET AL., *Drug Poisoning Deaths in the U.S., 1980-2008,* 81 NAT'L CTR. FOR HEALTH STAT DATA BRIEF, (2011); *See also* Md. Dep't of Health and Mental Hygiene Fact Sheet, *supra* note 50; CDC VITAL SIGNS, *supra* note 7.

[54] Md. Dep't of Health and Mental Hygiene, *Drug and Alcohol Intoxication Deaths in Md., 2007-2011*, http://dhmh.maryland.gov/vsa/Documents/Drug-and-Alcohol-Report-v5.pdf (last visited Sept. 13, 2015).

[55] *Id.*

in Maryland increased by 54 percent however in 2012.[56] With respect to demographics, the largest increases in fatal heroin-related overdoses in Maryland have been among younger age groups with a 53 percent increase identified among persons age 15-24 and a 59 percent increase identified among persons age 35-44.[57] Increases in heroin-related deaths have also been relatively proportional among Caucasian (42 percent) and African Americans (43 percent) as well as men (40 percent) and women (46 percent).[58]

Opioid overdose occurs when opioid levels in the body render a person unresponsive to stimulation or cause their breathing to become inadequate.[59] Inadequate breathing results in oxygen starvation that eventually stops the functionality of the heart and brain, resulting in unconsciousness, coma, and possibly death.[60] Death is solely dependent upon an individual's inability to breathe and maintain oxygen levels.[61] A survey of injection drug users found that approximately 50 percent experience at least one non-fatal overdose and 70 percent witness at least one overdose.[62] Further, despite the availability of life-saving treatment, victims of opioid overdose seldom receive timely assistance.[63] This may be due to a lack of or imperfect information regarding the symptoms of and how to treat an overdose,[64] fear of legal consequences for witnesses who were also engaging in drug use,[65] or a lack of access to naloxone.

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[56] *See generally* Press Release, *Public Health Update: State and Local Officials Respond to Increase in Heroin Overdoses,* MD. DEP'T OF HEALTH AND MENTAL HYGIENE (July 10, 2013), http://dhmh.maryland.gov/newsroom1/Pages/Public-Health-Update-State-and-Local-Officials-Respond-to-Increase-in-Heroin-Overdoses.aspx (reporting on the number of heroin-related deaths in Maryland in 2012).

[57] *See* Md. Department of Health and Mental Hygiene Fact Sheet, *supra* note 50.

[58] *Id.*

[59] Eliza Wheeler, ET AL., Harm Reduction Coal., *Guide to Developing and Managing Overdose Prevention and Take-Home Naloxone Projects*, 1, 9 (2012), http://harmreduction.org/wp-content/uploads/2012/11/od-manual-final-links.pdf (last visited Sept. 24, 2015)[hereinafter Harm Reduction Coalition].

[60] *Id.*

[61] *Id.*

[62] *See Staying Alive Drug Overdose Prevention and Response Plan*, BALT. CITY HEALTH DEP'T. http://health.baltimorecity.gov/node/2017 (last visited Sept. 23, 2015) [hereinafter *Baltimore Staying Alive Program*].

[63] Shane Darke & Deborah Zador, *Fatal Heroin 'Overdose': A Review*, 91 ADDICTION 1765, 1766–67 (1996).

[64] *See* Burris, *supra* note 13, at 287–88.

[65] *See generally* Catherine T. Baca, MD & Kenneth J. Grant, MD, *What*

Given these statistics, several states,[66] including, most recently, Maryland,[67] have implemented statewide opioid overdose response programs to educate participants on how to recognize the symptoms[68] of an opioid overdose.[69]

Naloxone hydrochloride has been marketed in the United States for over forty years under the trade name Narcan®.[70] Naloxone is the drug of choice used to counter the life-threatening symptoms of individuals having overdosed on heroin or prescription opioids.[71] Naloxone is not a controlled substance.[72] Rather, naloxone is a potent mu opioid receptor antagonist that attenuates the respiratory and central nervous system effects of heroin and prescription opioids.[73] Individuals who administered naloxone experience few side effects, with no negative side effects reported in healthy, opioid-free individuals.[74] Naloxone may be administered intramuscularly or intravenously[75] by emergency

Heroin Users Tell Us About Overdose, 26 J. ADDICTIVE DISEASES 63, 65–67 (2007) (finding that heroin users who witnessed an overdose hesitated in, or refrained from, calling an ambulance out of fear that the result would lead to someone being arrested).

66 *See generally* STATE PROGRAMS, *supra* note 9 (indicating that on October 1, 2013, Maryland enacted an overdose response program to be overseen by the Maryland Department of Health and Mental Hygiene).

67 *See generally* Md. Code Ann., Health–Gen. §§ 13-3101–09 (2014) (creating an opioid overdose response program by authorizing certain individuals to administer naloxone to an individual experiencing, or believed to be experiencing, opioid overdose to help prevent a fatality when medical services are not immediately available).

68 *See generally* Harm Reduction Coalition, *supra* note 59, at 57 (explaining that symptoms of an overdose include, but are not limited to, a person being awake but unable to talk, pale face, fingernails and lips turning blue or purplish-black, slow or erratic pulse, loss of consciousness, and unresponsiveness to outside stimuli).

69 Md. Code Ann., Health–Gen. § 13-3102 (2014); *See also* STATE PROGRAMS, *supra* note 9.

70 Daniel P. Wermeling, *A Response to the Opioid Overdose Epidemic: Naloxone Nasal Spray*, *in* 3 DRUG DELIVERY & TRANSLATIONAL RESEARCH. 63, 64 (2013) [hereinafter Wermeling].

71 *See* Harm Reduction Coalition, *supra* note 59, at 9.

72 21 C.F.R. § 1308.12(b)(1) (2015) (excluding naloxone from Schedule II classification).

73 *See* Harm Reduction Coalition, *supra* note 59, at 9 (detailing the respiratory and central nervous system effects of heroine).

74 *See generally* G.W. Terman, *Naloxone: Effects and Side Effects*, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM300866.pdf (last visited Sept. 22, 2015) (reviewing the effects and side effects of naloxone administration in patients with and without opioid use history).

75 *See* Harm Reduction Coalition, *supra* note 59, at 69 (explaining how naloxone may be administered).

medical personnel, physicians, and trained laypersons to reverse the effects of opioid overdose.[76]

III. MITIGATING THE LEGAL & PUBLIC HEALTH CONCERNS OF INCREASED ACCESS TO NALOXONE

Despite data demonstrating the growing public health concern of opioid overdose related deaths and the safety and effectiveness of naloxone in preventing these deaths, there are several legal barriers to increasing access to naloxone. The legal barriers associated with increased access to naloxone include the potential liabilities of physicians and/or nurse practitioners prescribing naloxone and its subsequent administration by non-patient third parties. Responding to these concerns, several states, including Maryland, have implemented state-based opioid overdose response programs[77] to mitigate the liabilities associated increased access to naloxone. As Maryland has most recently implemented a statewide opioid overdose response program, the legal concerns posed will be assessed in the context of Maryland law.

IV. PHYSICIAN & NURSE PRACTITIONER LIABILITY MARYLAND MEDICAL PRACTICE ACT

In all states, physicians may legally participate in overdose prevention programs by prescribing naloxone to drug users who are at risk of overdosing.[78] Naloxone is a prescription drug as opposed to a controlled substance[79] and is therefore subject to Maryland laws governing prescription medications. Pursuant to the Maryland Medical Practice Act,[80] prescribing medications is central to the practice of medicine.[81] In addition to prescribing medications, physicians[82] and/or nurse practitioners[83] may

[76] *Id.* at 9.

[77] *See* Md. Code Ann., Health–Gen. § 13-3101–09 (2014). *See also* STATE PROGRAMS, *supra* note 9 (listing state-based opioid overdose response programs).

[78] *See* Burris, *supra* note 13, at 273, 292.

[79] 21 C.F.R. § 1308.12(b)(1) (2015).

[80] MD. CODE ANN., HEALTH OCC. §§ 14-101(o)(2)(i) (2014).

[81] *Id.*

[82] *See generally* MD. CODE ANN., HEALTH OCC. § 12-102(c)(2)(ii)(1) (2014) (indicating that a physician may prepare and dispense prescription medications to their patients). *See also* MD. CODE REGS. 10.13.01.04(c) (2015).

[83] MD. CODE ANN., HEALTH OCC. §§ 8-508(a)–(b) (2010); MD. CODE REGS. 10.27.07.10(A) (2015) (indicating that a nurse practitioner may prescribe and

dispense prescription medications, however, physicians and nurse practitioners may only dispense prescription medications to their patients.[84] Further, nurse practitioners may only prescribe and dispense medications to patients at specified locations including medical or public health facilities and health centers.[85]

Subject to the rules, regulations and orders of the Maryland Board of Physicians,[86] physicians are also authorized to delegate[87] some of their medical duties, including the preparation and administration of prescription medications with[88] or without onsite supervision.[89,90] A physician may not however simply abdicate their duties. Pursuant to COMAR 10.32.12.03A, a delegating physician is required to

> (1) Evaluate the risk to the patient and the outcome of the delegated acts; (2) Delegate only those technical acts that are

personally prepare and dispense any medications that a nurse practitioner is authorized to prescribe in the course of treating a patient).

[84] *See* Legal Restrictions Relating to Proposed Naloxone Distrib. Program, 88 Op. Att'y Gen. MD 92 (2003) http://www.oag.state.md.us/Opinions/2003/88oag88.pdf [hereinafter Attorney General's Opinion].

[85] MD. CODE ANN., HEALTH OCC. § 8-508(c) (West 2010) *amended by* 2010 Md. Laws 78; COMAR 10.27.07.10(A), www.dsd.state.md.us/comar/comarhtml/10/10.27.07.10.htm (last visited Sept. 24, 2015) (identifying the locations where a nurse practitioner may prescribe and dispense medications).

[86] What is the Md. Board of Physicians, http://www.mbp.state.md.us/pages/whatis.html (last visited Sept. 24, 2015) (explaining the Maryland Board of Physicians as a state agency with the authority to license and discipline physicians and other health care providers). Physicians and other health care providers may be subject to disciplinary actions, including a restriction or a loss of licensure for violating the Maryland Medical Practice Act); Md. Bd. Nursing, http://mbon.maryland.gov/Pages/default.aspx. In addition, The Maryland Board of Nursing is a state agency with the authority to license and discipline nurse practitioners. *Id.*

[87] MD. CODE ANN., HEALTH OCC. § 14-306(a) (West 2010) *amended by* 2013 Md. Laws 359.

[88] *See* COMAR 10.32.12.04D(2)(a), http://www.dsd.state.md.us/comar/comarhtml/10/10.32.12.04.htm (last visited Sept. 24, 2015) (indicating that the preparation and administration of intradermal, subcutaneous and intramuscular injections may be delegated by a physician and requires on-site supervision).

[89] *See id.* (indicating that the preparation and administration of oral drugs may be delegated by a physician and does not require on-site supervision).

[90] *See* COMAR 10.32.12.02B(6), http://www.dsd.state.md.us/comar/comarhtml/10/10.32.12.02.htm (last visited Sept. 24, 2015) (defining on-site supervision as "oversight exercised by a delegating physician who is present at the site and able to be immediately available in person during the course of the performance of a delegated act").

> customary to the practice of the supervising physician; (3) Delegate only those technical acts for which the assistant has been trained; (4) Be responsible for the acts of the assistant; and (5) Supervise the assistant.[91]

Maryland laws posed serious roadblocks to the implementation of a statewide opioid overdose response program due to the potential liabilities for physicians and nurse practitioners that may prescribe naloxone for administration by third-parties. For example, a physician would be unable to comply with COMAR 10.32.12.03A as they would likely be unable to evaluate the risks of naloxone administration to an overdose victim.[92] Further, a physician would likely be unable to supervise the delegated duty of administering naloxone to the aforementioned victim.[93] Thus, a physician or nurse practitioner would "essentially be prescribing and dispensing a prescription drug to treat an individual that the physician [or nurse practitioner] had never met . . . [therefore] the responsibility for diagnosing the overdose and administering the medication would have been delegated to the participant."[94] As such, a physician or nurse practitioner may be found to be aiding the third-party administrator in the unlicensed practice of medicine[95] with disciplinary action ranging from a reprimand to a revocation of licensure to practice.[96]

V. MARYLAND FOOD, DRUG, & COSMETIC ACT

In addition to potential violations of the Maryland Medical Practice Act, physicians and nurse practitioners who prescribe naloxone to third-party administrators may have incurred liability under the Maryland Food, Drug, and Cosmetic Act ("Act").[97] Before prescription medications can properly be dispensed, a patient must be given information about the medication's indications, uses, risks, and benefits.[98] The Act sets

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91 *See* Attorney General's Opinion, *supra* note 84, at 92.

92 *Id.* at 93.

93 *Id.*

94 *Id.* at 94.

95 MD. CODE ANN., HEALTH OCC. § 14-404(a)(18) (West, Westlaw through 2015); MD. CODE ANN., HEALTH OCC. § 8-316(a)(23) (West, Westlaw through 2014).

96 MD. CODE ANN., HEALTH OCC. § 14-404(a) (West, Westlaw through 2015); MD. CODE ANN., HEALTH OCC. § 8-316(a) (West, Westlaw through 2014).

97 MD. CODE ANN. HEALTH–GEN. §§ 21-201–63 (West, Westlaw through 2006).

98 *See* Burris, *supra* note 13, at 311.

forth requirements for dispensing prescription medications,[99] including that the use of prescription medications be supervised by a health care practitioner with authorization to administer medicine.[100] Thus, under the Act, naloxone could not properly be prescribed and dispensed to a third-party administrator as they would not be at risk of an overdose and therefore have no medical need for naloxone.[101] Further, naloxone would not be administered under the supervision of a health care practitioner, which contravenes the Act.[102] Pursuant to the Act, a drug that is improperly dispensed is also considered misbranded.[103] As such, a physician or nurse practitioner that dispenses a misbranded drug may be found in violation of the Act, convicted of a criminal misdemeanor, and subject to fines and additional civil penalties.[104]

VI. THIRD-PARTY ADMINISTRATOR LIABILITY

Similar to physicians and nurse practitioners, third-party administrators could be subject to criminal liability for administering naloxone to persons experiencing or believed to be experiencing an opioid overdose. In Maryland, a person must be licensed by the Board of Physicians in order to practice medicine.[105] As there is no provision that "explicitly permits a physician to delegate to an unlicensed person the authority to perform a future medical act on an unidentified individual or to administer a naloxone injection in the absence of the physician,"[106] a third-party administrator who administers naloxone may be considered as practicing medicine without a

[99] MD. CODE ANN. HEALTH–GEN. §§ 21-221(a)(1))–(5) (West, Westlaw through 1988); *See also* Attorney General's Opinion, *supra* note 84, at 95.

[100] MD. CODE ANN. HEALTH–GEN. § 21-220(a)(2) (West, Westlaw through 2006).

[101] *See* Burris, *supra* note 13, at 311.

[102] MD. CODE ANN., HEALTH–GEN. § 21-220(a)(2) (West, Westlaw through 2006); *See also* Attorney General's Opinion, *supra* note 84, at 95.

[103] MD. CODE ANN., HEALTH–GEN. § 21-220(d) (West, Westlaw through 2006).

[104] MD. CODE ANN., HEALTH–GEN. §§ 21-1215(b)(1)–(2) (West, Westlaw through 2004) (noting that violation is a criminal misdemeanor that carries a potential sentence of up to one year imprisonment and a fine of up to $10,000 with multiple violations carrying the possibility of an enhanced sentence of up to three years' incarceration and a fine of up to $25,000); MD. CODE ANN., HEALTH–GEN. § 21-1215(c) (West, Westlaw through 2004) (noting that a violation may result in civil penalties up to $5,000).

[105] MD. CODE ANN., HEALTH OCC. § 14-301 (West, Westlaw through 1997); MD. CODE ANN., HEALTH OCC. § 14-601 (West, Westlaw through 2013).

[106] *See* Attorney General's Opinion, *supra* note 84, at 96.

license.[107] By practicing medicine without a license, the third-party administrator would be subject to criminal liability.[108]

Although potentially subject to criminal liability, a third-party administrator would likely be immune from civil liability to a person experiencing an overdose pursuant to Md. Code Ann., Cts. & Jud. Proc. Art. § 5-603(c).[109] Section 5-603(c) provides that an individual will not be liable for providing assistance or medical aid to a victim at the scene of an emergency, if the aid is uncompensated and provided in a reasonably prudent manner.[110]

VII. INCREASING ACCESS & DECREASING LIABILITY: STATE & COMMUNITY-BASED OPIOID OVERDOSE RESPONSE PROGRAMS

Recognizing the importance of preventing opioid overdose related deaths, opioid overdose response programs, training individuals how to administer naloxone were initiated in the United States in 1996.[111] As of 2010, there were 188 community-based opioid overdose response programs providing naloxone in 15 different states and the District of Columbia.[112] The principle underlying the development of these programs is that death from opioid overdose can be prevented as there is a temporal window in which an overdose can be reversed via naloxone administration.[113] Thus, the overall goal of opioid overdose response programs is to create a comprehensive community-based program that provides education on overdose prevention and instruction on practical intervention.[114] Since 1996, 53,032 individuals have been trained how to properly administer naloxone with 10,171 opioid overdose reversals reported.[115]

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107 *See* Burris, *supra* note 13, at 328.

108 MD. CODE ANN., HEALTH OCC. § 14-606(a)(1)–(5) (West, Westlaw through 2013) (the unauthorized practice of medicine may be punishable by imprisonment and a fine up to $50,000).

109 *See* Attorney General's Opinion, *supra* note 84, at 98.

110 *Id.*; *See also* MD. CODE ANN., CTS. & JUD. PROC. § 5-603(c) (West, Westlaw through 2015).

111 Eliza Wheeler, *Take-Home Naloxone for Opiate Overdose: Exploring the Legal, Policy and Practice Landscapes*, HARM REDUCTION COAL. (Oct. 18, 2012), http://harmreduction.org/overdose-prevention/overdose-news/take-home-naloxone-for-opioid-overdose-exploring-the-legal-policy-and-practice-landscapes/ [hereinafter Take-Home].

112 *See* Harm Reduction Coalition, *supra* note 59, at 17.

113 *See* Take-Home, *supra* note 111.

114 *See Baltimore Staying Alive Program*, *supra* note 62.

115 *See* Take-Home, *supra* note 111.

An impetus to the establishment of statewide opioid overdose response programs were community-based programs such as the Baltimore Staying Alive Program.[116] In 2004, the Baltimore Staying Alive Program was developed by the Baltimore City Health Department in response to the rate of drug overdose deaths in Baltimore City.[117] The program educates drug users about opioid overdose and trains drugs users how to identify and treat an opioid overdose by administering resuscitation measures and naloxone.[118] Participants in the Baltimore Staying Alive Program are recruited via the Baltimore City Needle Exchange Program[119] or substance abuse centers throughout Baltimore.[120] The program has five operational sites, each with a volunteer physician that prescribes naloxone to program participants.[121] Volunteer physicians meet with each participant to review their medical history and evaluate the risks of prescribing naloxone to the participant.[122] Following a determination of the participant's eligibility to receive a naloxone prescription, the participant receives an overdose prevention kit including intramuscular syringes, naloxone, a rescue breathing mask, and a sharps container to dispose of the needles/syringes.[123]

The effectiveness of the Baltimore Staying Alive Program has been reported by the Baltimore City Health Department. Since its inception, the Baltimore Staying Alive Program has trained more than 3,700 participants and more than 220 opioid overdose reversals have been reported.[124] An additional study conducted by Tobin and colleagues evaluated the effectiveness of the Baltimore Staying Alive Program among a cohort of forty-three participants as related to teaching injection drug users (1) how to recognize the signs and symptoms of an opioid overdose; (2) how to administer naloxone; (3) basic facts about naloxone; and (4)

116 *See Baltimore Staying Alive Program*, *supra* note 62.

117 *Id.*

118 *Id.*

119 *See* Balt. City Health Dep't Needle Exchange Program, BALT. CITY HEALTH DEP'T, http://health.baltimorecity.gov/hiv-std-services/community-risk-reduction (last visited Sept. 30, 2015).

120 Chris Serio-Chapman, *Staying Alive Program Overdose Prevention and Mgmt.*, http://mail.a-pdf.com/tags/alive%20program/1 (last visited Sept. 28, 2015) [hereinafter *Staying Alive Program*].

121 *Id.*

122 *Id.*

123 *Id.*

124 *Id.*; *see also Baltimore Staying Alive Program*, *supra* note 62.

opioid overdose prevention strategies.[125] Data revealed that the Baltimore Staying Alive Program increased the use of naloxone during opioid overdose, yielding twenty-two opioid overdose reversals by nineteen individuals.[126] Further, post-training, study participants demonstrated an increased knowledge about naloxone, including the risk of overdose relapse after revival.[127] Taken together, data from this study provided further support for the utility of opioid overdose response programs and increased access to naloxone.

Given the success of the Baltimore Staying Alive Program, and in an effort to further prevent opioid overdose related fatalities in Maryland, Governor Martin O'Malley approved the enactment of Senate Bill 610 (SB 610) on May 2, 2013.[128] SB 610 established a statewide opioid overdose response program overseen by the Department of Health and Mental Hygiene (DHMH).[129] The purpose of enacting SB 610 was to help prevent and/or reduce the number of fatalities from opioid overdose when EMS personnel are not immediately available.[130] Thus, the program authorizes certain individuals (certificate holders) to administer naloxone to an individual experiencing, or believed to be experiencing, an opioid overdose.[131]

The program, an extension of the Baltimore Staying Alive Program,[132] also addresses the legal concerns facing physicians, nurse practitioners, and third-party administrators with respect to prescribing, dispensing, and administering naloxone. The Maryland opioid overdose response program enables physicians and nurse practitioners to prescribe and dispense naloxone to certificate holders that have successfully completed an educational training program.[133] The educational training

125 Karin Tobin et al., *Evaluation of the Staying Alive Programme: Training injection drug users to properly administer naloxone and save lives*, 20 INT'L J. OF DRUG POL'Y 131, 132 (2009).

126 *Id.* at 135.

127 *Id.* at 134.

128 For detailed information regarding the review and approval of S. 610, 2013 Leg., (MD. 2013), *see* Maryland General Assembly http://mgaleg.maryland.gov/webmga/frmMain.aspx?pid=billpage&stab=03&id=sb0610&tab=subject3&ys=2013RS.

129 S. 610, 2013 Leg., (Md. 2013); MD. CODE ANN., HEALTH–GEN. §§ 13-3101–09 (2014).

130 MD. CODE ANN., HEALTH–GEN. § 13-3102 (West, Westlaw through 2015).

131 MD. CODE ANN., HEALTH–GEN. § 13-3107 (West, Westlaw through 2014).

132 *See Baltimore Staying Alive Program*, *supra* note 62.

133 MD. CODE ANN., HEALTH–GEN. §§ 13-3101–09 (West, Westlaw through 2014).

program includes instruction related to the recognition of the symptoms of an opioid overdose, proper administration of naloxone, the importance of contacting EMS, and care for the person experiencing an overdose following naloxone administration.[134] To qualify for a certificate, an individual shall be at least eighteen years old and have, or reasonably expect to have, the ability to assist a person experiencing an opioid overdose via naloxone administration.[135]

Following successful completion of the training program, a licensed physician or nurse practitioner may prescribe naloxone and the supplies necessary for its administration to the certificate holder.[136] Naloxone may then be administered by the certificate holder in emergency situations when EMS personnel are not immediately available.[137] Under the program, physicians may not be subject to any disciplinary action under Title 14 of Maryland's Health Occupations Article[138] for prescribing or dispensing naloxone to a certificate holder.[139] Further, certificate holders administering naloxone to a person experiencing or believed to be experiencing an opioid overdose may not be considered as practicing medicine.[140,141] As such, Maryland's opioid overdose response program dispels the concerns of physicians, nurse practitioners and certificate holders participating in the program regarding liabilities for prescribing, dispensing and administering naloxone and therefore increases access to naloxone.

VIII. PUBLIC HEALTH CONCERNS REGARDING INCREASED ACCESS TO NALOXONE

In addition to the legal challenges underlying increased access to naloxone, there are also several public health concerns. A major cause for opposition to increasing naloxone access is the safety of administration by unlicensed persons and lack of follow-

134 MD. CODE ANN., HEALTH–GEN. § 13-3104(d)(2) (West, Westlaw through 2015).
135 *Id.* at § 13-3104(a)–(d).
136 *Id.* at § 13-3108.
137 *Id.* at § 13-3102.
138 *Id.* at § 13-3109(b).
139 *See id.*
140 MD. CODE ANN., HEALTH–GEN. § 13-3109(a) (West, Westlaw through 2015).
141 MD. CODE ANN., HEALTH–O.C.C.. §§ 14-301, 14-601 (West, Westlaw through 2015).

up care for overdose victims.[142] For example, certificate holders may prematurely administer naloxone due to a lack of understanding of the half-life of the drug, thus resulting in overdose due to recurrence of respiratory depression.[143] Additionally, drug users may prematurely administer opioids to counter the symptoms of withdrawal precipitated by naloxone.[144]

This argument however finds no merit in the empirical data. For example, a study of third-party naloxone administration in Chicago revealed no cases of opioid overdose that required a second administration of naloxone to counter a recurrence of overdose symptoms.[145] In addition, Green and colleagues determined that trained drug users were as adept as medical personnel in identifying the signs of an opioid overdose and determining whether administration of naloxone was needed.[146] Data also suggests that premature injection of opioids was not a problem among overdose patients having been revived with naloxone[147] and there are no documented cases of medical problems associated with the re-administration of opioids following treatment with naloxone.[148]

Opponents of increased access to naloxone also argue the necessity of maintaining the status quo as the increased availability of naloxone and those trained to administer it facilitates drug use by acting as a safety-net for drug users.[149] This argument also finds no support in the literature; rather it facilitates the stigmatization[150] associated with drug abuse. Empirical studies addressing this argument suggest that the increase in overdose awareness via opioid overdose training programs reduces opioid use and increases a drug user's desire to

142 Daniel Kim et al., *Expanded Access to Naloxone: Options for Critical Response to the Epidemic of Opioid Overdose Mortality*, AM. J. OF PUB. HEALTH, Vol. 99, No. 3, 402–07 (March 2009) [hereinafter Kim]; *see also id.* at 403–04 nn.6, 17, & 38.

143 *See* Kim, *supra* note 142, at 404.

144 *Id.*

145 *Id.*

146 T.C. Green et al., *Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States*. 6 ADDICTION, Jun; 103(6) 979–89 (2008), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163671/ (last visited Oct. 6, 2015).

147 *See* Kim, *supra* note 142, at 404.

148 *Id.*

149 *Id.*

150 *See* Link, *supra* note 35, at 179–80.

seek treatment.[151]

The public health concerns associated with expanded access to naloxone are strikingly similar to those voiced by opponents to switching the oral contraceptive, Plan B, from a prescription medication to an OTC medication. Although opponents to the Plan B switch, which would increase access to Plan B, cited safety concerns as the driving force underlying their opposition (similar to naloxone), scholars maintain that the opposition was moral, rather than biological, in nature.[152] For example, opponents to the Plan B switch contended that increased access to Plan B would increase promiscuity and risky behaviors while decreasing adolescents seeking testing for and protection from sexually transmitted diseases.[153] Empirical data however demonstrated no increase in sexual promiscuity, unprotected sex, sexually transmitted diseases or decrease in the use of contraceptives;[154] similar to the data generated for naloxone.

An additional concern of opponents to increased access to naloxone is cost. At present, the cost of providing naloxone is not a prohibitive factor to overdose response programs. The price of naloxone kits can range from $15 to $30 per kit.[155] Additional costs incurred would be the result of any educational materials provided or training costs. Empirical data demonstrates however that opioid overdose response programs are cost-effective.[156] Of concern however are reports indicating that the cost of naloxone is rising due to the paucity of manufacturers producing naloxone and its prescription status.[157]

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151 *See* Kim, *supra* note 142, at 404 nn.6, 17, & 38.

152 Roseann B. Termini & Miranda Lee, *Sex, Politics, and Lessons Learned from Plan B: A Review of the FDA's Actions and Future Direction* 36 OKLA. CITY U. L. REV. 351, 364 (2011).

153 *Id.* at 365 (citing Tummino v. Torti, 603 F. Supp. 2d 519, 528 (E.D.N.Y. 2009)).

154 *Id.* (citing *Tummino*, 603 F. Supp. 2d at 528; JUDITH A. JOHNSON ET AL., CONG. RESEARCH SERV., RL 33728, EMERGENCY CONTRACEPTION: PLAN B 4–5 (2006); U.S. Gov't Accountability Office, GAO-06-109, *Food and Drug Administration: Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual* 7 (2005), http://www.gao.gov/new.items/d06109.pdf).

155 Phillip Coffin & Sean Sullivan, *Cost-effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal*, 158 ANNUALS INTERNAL MED. 1, 3 (2013) (discussing the average cost of naloxone kits).

156 *Id.* at 1.

157 *See* Maia Szalavitz, *Overdose Drug's 1000% Price Hike Sparks Outrage*, THE FIX (April 11, 2013), http://www.thefix.com/content/naloxone-price-hospira-protests-FDA91528 [hereinafter Szalavitz].

IX. FEDERAL INTERVENTION TO SAVE LIVES

Naloxone is a safe and effective medication for treating opioid-related overdose. "Naloxone has been available as an OTC medication in Europe since the 1980's without any reported negative outcomes."[158] The legal and public health concerns related to opioid overdose response programs and expanded access to naloxone are due primarily to the FDA's classification of naloxone as a prescription drug and its current injectable formulation. To alleviate these concerns, advocates have proposed that the FDA approve a switch in naloxone's prescription status so that it may be marketed as an OTC medication and/or approve an intranasal formulation for use in non-medical settings.[159] There are several regulatory requirements however that must be addressed prior to the approval of a prescription-to-OTC switch of naloxone and/or approval of an intranasal formulation.

X. FDA OVERSIGHT OF PRESCRIPTION & OTC DRUGS

The FDA takes great care in seeking to protect consumers from the potential deleterious effects of medications. The Food, Drug, and Cosmetic Act (FDCA),[160] provides the FDA the statutory authority to regulate drugs.[161] Pursuant to the FDCA, the FDA may determine that specific drugs require a prescription due to their

> [T]oxicity or other potentiality for harmful effect . . . the method of its use . . . the collateral measures necessary to its use, is not safe

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158 *See* Kim, *supra* note 142 (citing Scott Burris et al., *Legal Aspects of Providing Naloxone to Heroin Users in the United States*, 12 INT'L J. OF DRUG POL'Y 237, 242 (2001); S. Galea, et al., *Provision of naloxone to injection drug users as an overdose prevention strategy: Early evidence from a pilot study in New York City*, 31 ADDICT BEHAV. 907, 908 (2006)).

159 *See generally* Burris, *supra* note 13, at 330-40 (discussing possibilities and obstacles to intranasal formulation of naloxone).

160 *See* Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 (1938) (providing the sections of Title 21 of the U.S.C. referencing the FDAC).

161 *See* 21 U.S.C. § 321(g)(1) (2009) (defining the term drug as "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)").

> for use except under the supervision of a practitioner licensed by law to administer such drug; or is limited by an approved application . . . to use under the professional supervision of a practitioner licensed by law to administer such drug.[162,163]

Thus, if drugs pose a safety risk to consumers self-administering the drugs, they must be made available only by prescription.[164]

As prescription medications require the supervision of a licensed physician, they are exempt from the strict labeling requirements applicable to OTC medications.[165] To ensure proper labeling and avoid misbranding, prescription drug labels must include the "name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber,… the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription"[166] and the symbol "Rx only."[167] Although not requiring detailed directions for consumer use,[168] prescription drug labels must provide full disclosure to the licensed healthcare professional allowed to administer the drug.[169] Doing so helps to ensure that the healthcare professional not only selects the appropriate drug for the patient but safely instructs the patient on how to use the drug.[170]

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[162] 21 U.S.C. § 353(b) (2015).

[163] *See* Holly M. Spencer, *The Rx-to-OTC Switch of Claritin, Allegra, and Zyrtec: An Unprecedented FDA Response to Petitioners and the Protection of Public Health*, 51 AM. U. L. REV. 999, 1014 (2002)[hereinafter Spencer] (citing *United States v. Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980) (stating that "[s]ince a prescription drug…can be used only under a physician's supervision…such a drug must qualify for a regulatory exemption created by FDA. By providing for such exemptions, Congress apparently anticipated that certain classes of drugs might be unable to meet an adequate direction for lay use requirement.")).

[164] *Id.*; *see also* 21 U.S.C. § 353(b)(1)(A) (2015).

[165] *See* Spencer, *supra* note 163; *see also* 21 U.S.C. § 352(f) (2013).

[166] *See* Spencer, *supra* note 163, at 1015; s*ee also* 21 U.S.C. § 353(b)(2) (2015) (identifying the labeling requirements for prescription drugs).

[167] *See* Spencer, *supra* note 163; *see also* 21 U.S.C. § 353(b)(4)(A) (2015) (indicating that a prescription drug will be "deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol 'Rx only.'").

[168] *See* Spencer, *supra* note 163, at 1015; *see also* 21 C.F.R. § 201.100 (exempting prescription drugs from labeling that provides adequate directions for use).

[169] *See* Spencer, *supra* note 163, at 1015; *see also* 21 C.F.R. § 201.56 (identifying the content and format requirements for prescription drug labels).

[170] *See* Spencer, *supra* note 163.

In addition regulating prescription drugs, the FDA also has the authority to designate certain drugs that are generally recognized as safe[171] and effective[172] and not misbranded, OTC status.[173] To determine whether a drug should be designated OTC status, the Commissioner of the FDA appoints advisory panels with the requisite expertise necessary to evaluate the safety and effectiveness of potential OTC drugs.[174] In evaluating whether a potential OTC drug is safe and effective under the prescribed, recommended or suggested conditions of use, the advisory panel considers marketing studies and controlled clinical investigations.[175] Doing so allows the advisory panel to appropriately assess the benefit-to-risk ratio of a drug to the consumer.[176]

In addition to evaluating the safety and effectiveness of OTC

[171] 21 C.F.R. § 330.10(a)(4)(i) (defining safety as a "low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability."). "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use . . .This proof shall include results of significant human experience during marketing … General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data." *Id.*

[172] *Id.* at § 330.10(a)(4)(ii) (defining effectiveness as "a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed."). "Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness." *Id.* "Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing … Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered … General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data." *Id.*

[173] *See generally* 21 C.F.R. § 330.1 (identifying the general conditions for general recognition of a drug as being safe, effective and not misbranded).

[174] *See generally* 21 C.F.R. § 330.10 (identifying the procedures required for evaluating the safety, effectiveness, and labeling of OTC drugs and for establishing drug monographs).

[175] *See generally id.* at § 330.10(a)(4)(i)–(ii) (mandating that "[t]he advisory review panel, in reviewing data submitted to it and preparing conclusions and recommendations…shall apply the [] standards" outlined in subsections (i) and (ii)).

[176] *Id.* at § 330.10(a)(4)(iii).

drugs, the advisory panels also review OTC drug labels.[177] OTC drugs have very distinct labeling requirements as compared to prescription drugs.[178] OTC drug labels must clearly describe, in comprehensible language, the information necessary to instruct an individual on how to properly use the drug, results anticipated from its use, warnings against unsafe use and any potential adverse reactions associated with the drug's consumption.[179] Thus, in addition to ensuring the safety and effectiveness of OTC drugs, the FDA, through labeling regulations, seeks to educate consumers about the proper use and side effects of OTC drugs in order to limit and deter product misuse.[180]

In addition to direct-to-OTC marketing, the FDA has the authority to determine that an approved drug, such as naloxone, no longer requires a prescription and may be switched from prescription-to-OTC and marketed as OTC.[181] A drug may be switched from prescription to OTC if the FDA Commissioner finds that prescription requirements are not needed for the drug for the protection of the public health because the drug is safe and effective for use in self-medication, as directed in the proposed label.[182] In addition to unilateral action by the FDA Commissioner, the prescription-to-OTC switch process can be initiated by any interested person by filing a petition[183,184]

[177] *Id.* at § 330.10(a)(1).

[178] *See generally* 21 C.F.R. § 201.66 (outlining the format and content requirements for OTC drug product labeling).

[179] 21 C.F.R. § 330.10(a)(4)(v); *see also* Spencer, *supra* note 163, at 1012.

[180] *See* Spencer, *supra* note 163, at 1012.

[181] 21 U.S.C. § 353(b)(3) (identifying that when it is no longer necessary for the protection of the public health, drugs may be exempted from prescription status).

[182] *See* Spencer, *supra* note at 163, at 1016; *see also* 21 C.F.R. § 310.200(b) ("Prescription-exemption procedure for drugs limited by a new drug application. 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. Any interested person may file a petition seeking such exemption, which petition may be pursuant to part 10 of this chapter, or in the form of a supplement to an approved new drug application.")

[183] *See generally* 21 C.F.R. § 10.30 (providing information related to the

seeking exemption of the drug from its prescription status or by filing a supplement to an approved New Drug Application (NDA).[185]

XI. INCREASING ACCESS TO NALOXONE VIA AN INTRANASAL FORMULATION AND/OR A PRESCRIPTION-TO-OTC SWITCH

Researchers and scholars have suggested that a potential way to expand access to naloxone is to increase the number of formulations available to consumers.[186,187] Some EMS programs are already using existing technologies of the approved drug and an existing medical device to administer naloxone, albeit in a non-FDA-approved manner.[188] Here, EMS personnel use the FDA-approved injectable formulation (1 mg/mL) of naloxone and administer 1 mL per nostril via a marketed nasal atomizer/nebulizer device (Mucosal Atomization Device).[189] As such, it has been proffered that an intranasal formulation be developed as an alternative to injectable naloxone which can prevent the potential harms associated with third-party administrators giving overdose victims intramuscular injections.[190]

Intranasal spray medications designed for systemic absorption target the turbinates on the medial wall of the nasal cavity.[191] In ideal circumstances, most of the administered drug is absorbed into the bloodstream within fifteen to twenty minutes.[192] Nasally

petitions filed by interested parties seeking a prescription-to-OTC switch).

184 21 C.F.R. § 310.200(b).

185 *Id.*

186 *See* Compton, *supra* note 2; *see also* Burris, *supra* note 13.

187 *See* Wermeling, *supra* note 70.

188 *Id.* at 73 (citing E.D. Barton et al., *Efficacy of Intranasal Naloxone as a Needleless Alternative to Treatment of Opioid Overdose in the Prehospital Setting*, 29 J. EMERGENCY MED. 265 (2005); E.D. Barton et al., *Intranasal Administration of Naloxone by Paramedics*, 6 PREHOSPITAL EMERGENCY CARE 54 (2002)).

189 *Id.*

190 *See generally* Needlestick Safety and Prevention Act, H.R. 5178, 106th Cong. § 2(7) (2000) (finding that "the use of safer medical devices, such as needless systems and sharps with engineered sharps injury protections…can be extremely effective in reducing accidental sharps injuries.").

191 *See* Wermeling, *supra* note 70, at 66.

192 *Id.* at 65 (citing H.R. Constantino et al., *Intranasal Delivery: Physicochemical and Therapeutic Aspects*, 337 INT'L J. PHARMACEUTICS 1 (2007); S. Grassin-Delyle et al., *Intranasal Drug Delivery: An Efficient and Non-invasive Route for Systemic Administration*, 134 PHARMACOLOGY &

administered drugs that are not completely absorbed following administration may also undergo a second (oral) absorption phase.[193] Due to its high water solubility, naloxone is an ideal candidate for intranasal delivery and satisfies a variety of criteria necessary for this route of administration.[194] Naloxone is also a high first-pass metabolism medication with an oral bioavailability reported to be ≤5 percent.[195]

Although a viable option for intranasal delivery, the pharmacokinetic profile of intranasal naloxone (i.e. a highly concentrated nasal solution formulation) in humans is not well described.[196] Physicians and EMS personnel however have extensive clinical experience with intranasal naloxone administration. Loimer and colleagues[197] reported that delivery of naloxone (1 mg) intranasally was as effective as intravenous administration in identifying persons that were physically dependent on opioids. The utility of intranasal naloxone when used by paramedics has also been reported by Barton and colleagues.[198] Here, 30 patients received 2 mg of the injectable form of naloxone (1 mg/mL) via intranasal administration (1 mL per naris).[199] Data from this study indicated that 83 percent of patients with an opioid overdose responded to intranasal naloxone, with an average response time of 3.4 minutes, suggesting the utility of nasal delivery of naloxone in clinical practice.[200] With respect to safety and effectiveness, a randomized, controlled, open label trial investigating the adverse events following administration of a specially prepared concentrated form of naloxone (2 mg/mL) delivered intranasally or intramuscularly has been conducted.[201] Data from this study revealed that the adverse events experienced by persons having

THERAPEUTICS 366 (2012)).

193 *Id.* at 65–66.

194 *Id.* at 66.

195 *Id.* at 67.

196 *See* Wermeling, *supra* note 70, at 68.

197 *See id.* at 69 (citing N. Loimer et al., *Nasal Administration of Naloxone for Detections of Opiate Dependence*, 26 J. PSYCHIATRIC RES. 39 (2011); N. Loimer et al., *Nasal Administration is as Effective as the Intravenous Route in Opiate Addicts*, 19 INT'L J. MENTAL HEALTH & ADDICTION 819 (1994)).

198 *See id.* at 70 (citing E.D. Barton et al., *Efficacy of Intranasal Naloxone as a Needleless Alternative to Treatment of Opioid Overdose in the Prehospital Setting*, 29 J. EMERGENCY MED. 265 (2005)).

199 *Id.* at 70.

200 *Id.*

201 *Id.* at 71 (citing D. Kerr et al., *Intranasal Naloxone for the Treatment of Suspected Heroin Overdose*, 103 ADDICTION 379 (2008)).

overdosed on heroin did not differ depending on the route of naloxone administration and were generally mild (agitation, nausea and vomiting).[202]

Although a potentially viable option for easier administration and expanded access to naloxone there are regulatory challenges related to the development of an intranasal formulation that preclude it from being immediately available as either a prescription or an OTC drug. Naloxone is a post-patent generic drug[203] and a new, intranasal formulation would require the filing of an NDA[204] with the FDA. Although the active ingredient in the intranasal formulation would not change, it is likely that the dosage of an intranasal formulation would differ from the injectable form. Thus, approval for intranasal naloxone could not be sought under an Abbreviated NDA.

There are two regulatory pathways in which an NDA can be submitted for review by the FDA.[205] An NDA submitted under § 505(b)(1)[206] is required for a new drug whose active ingredient has not previously been approved.[207] An NDA submitted under § 505(b)(1) requires extensive data developed by the applicant demonstrating the safety and effectiveness of the drug for its proposed indication(s), adequate production methods for the drug and that the proposed labeling be appropriate.[208] In contrast, an

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[202] *See* Wermeling, *supra* note 70, at 72.

[203] *See* LEO BELETSKY ET AL., TEMP. U. HEALTH L., POLITICS, & POL'Y CENTER, CLOSING DEATH'S DOOR: ACTION STEPS TO FACILITATE EMERGENCY OPIOID DRUG OVERDOSE REVERSAL IN THE UNITED STATES, CONFERENCE REPORT 17 (2009) [hereinafter Beletsky].

[204] *See generally* 21 U.S.C. § 355(b) (West, Westlaw through P.L. 113-5 approved 03/11/13) (stating that NDA would be required if a petition for an Abbreviated NDA were denied).

[205] *Id.*

[206] *Id.* at § 355(b)(1).

[207] *Id.* at § 355(a).

[208] *Id.* at § 355(b)(1) (The requirements of an NDA submitted under this section include "(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the

applicant that submits an NDA under § 505(b)(2) may rely on data developed by others (i.e. published literature or the FDA's previous findings of safety and effectiveness) to support their application.[209] The FDA seeks a scientific bridge, such as comparative bioavailability data, however to determine if it is rational to rely on published literature or prior findings of safety and effectiveness to support a § 505(b)(2) application.[210]

In April, 2012, the FDA addressed some of the regulatory concerns associated with the development of an intranasal naloxone formulation.[211] At the meeting, there were several recommendations identified to support an NDA for intranasal naloxone. The FDA noted that the first critical step in approving intranasal naloxone would be determining whether the intranasal formulation is bioequivalent to the injectable formulation.[212] In assessing bioequivalence, the FDA noted the importance of conducting studies where at least two doses of the intranasal formulation would be compared to the approved naloxone formulation and route of administration.[213] The goal of these studies is to "target the plasma naloxone levels to be detectable and comparable and present for a meaningful duration relative to the approved product."[214] Upon determining bioequivalence, additional criteria noted by the FDA for intranasal naloxone would include whether the intranasal device has been approved by the Center for Devices and Radiologic Health,[215] characteristics of the product being distributed by the device[216] and whether the product can be used by its intended

manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences."; *see also* FDA, NDA 505(b)(1) of the FD&C Act, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM245363.pdf (last visited Oct. 12, 2015) [hereinafter NDA 505(B)(1) INFORMATION].

209 21 U.S.C. § 355(b)(2); *see also* NDA 505(B)(1) INFORMATION, *supra* note 208.

210 *See* FDA MEETING TRANSCRIPT, *supra* note 14, at 165.

211 *See id.*

212 *Id.* at 167.

213 *Id.* at 169–70.

214 *Id.* at 170.

215 *Id.* at 167.

216 *See* FDA MEETING TRANSCRIPT, *supra* note 14, at 168.

population[217] (i.e. patients or third-party administrators).

In addition to providing information regarding the regulatory requirements necessary for an intranasal formulation of naloxone to be considered for approval, the FDA also provided an overview the requirements necessary to support a prescription-to-OTC switch of naloxone.[218] The FDA noted switching naloxone from prescription-to-OTC would require an NDA.[219] Further, the FDA noted that having an industry partner generate data to support an NDA would be a more expeditious process than the rulemaking process (which requires unilateral action by the FDA Commissioner or a citizen's petition, in addition to data similar to that needed to support an NDA, to establish or amend an existing drug monograph).[220] Thus, the FDA will take a "fresh look" at naloxone including "all of the components of the prescription NDA and then some."[221] In addition to a review of naloxone's approved NDA, switching to an OTC formulation would also require consumer studies to demonstrate that naloxone could be used safely and effectively in an OTC setting.[222]

Required consumer studies for naloxone would include a label comprehension study to determine whether consumers can understand the label and whether the label communicates messages essential to naloxone's use.[223] Given there is training involved in the use of naloxone, a human factors study would also be required to determine whether consumers can adequately follow the directions for use.[224] Self-selection studies would also

[217] *Id.* at 167.

[218] *Id.*; *see also* ANDREA LEONARD-SEGAL, FDA, NALOXONE EXPANDED ACCESS: OTC STATUS CONSIDERATIONS FOR A NONPRESCRIPTION DRUG DEVELOPMENT PROGRAM 1, 3–4 http://www.fda.gov/Drugs/NewsEvents/ucm277119.htm (follow "Naloxone Expanded Access: OTC Status Considerations for a Nonprescription Drug Development Program") (Apr. 12, 2012) [hereinafter SEGAL PRESENTATION].

[219] *See* FDA MEETING TRANSCRIPT, *supra* note 14, at 181.

[220] *See* SEGAL PRESENTATION, *supra* note 218.

[221] *Id.* at 15–17 (indicating that the FDA would review the chemistry, pharmacology, toxicology, microbiology, clinical pharmacology, safety, efficacy, consumer studies and labeling of an OTC formulation).

[222] *See* SEGAL PRESENTATION, *supra* note 218, at 16; *see generally* FDA MEETING TRANSCRIPT, *supra* note 14, at 184–88 (stating that there are four different consumer studies and describing each study, in turn).

[223] *See* SEGAL PRESENTATION, *supra* note 218, at 16, 19–21; *see also* FDA MEETING TRANSCRIPT, *supra* note 14, at 184–85.

[224] *See* SEGAL PRESENTATION, *supra* note 218, at 19, 22; *see also* FDA MEETING TRANSCRIPT, *supra* note 14, at 185–86.

need to be conducted to determine whether consumers can properly identify whether or not naloxone is needed (i.e. can consumers recognize the signs and symptoms of an opioid overdose).[225] Naloxone would also require an actual-use study/clinical trial prior to OTC approval to determine whether naloxone would be used safely and properly in an OTC setting.[226] Thus, although a potentially viable option for easier administration and expanded access to naloxone, there are a number of regulatory requirements that must be met prior to the development of intranasal naloxone and/or its approval as an OTC drug.

XII. PAVING THE WAY FOR INCREASED ACCESS: CAN THE FEDERAL GOVERNMENT STIMULATE INDUSTRY INTEREST IN NALOXONE?

Although the federal government-sponsored meeting[227] provided recommendations for a regulatory pathway for developing an intranasal naloxone formulation or switching its status from a prescription-to-OTC, the largest challenge precluding increased access to naloxone is the pharmaceutical industry. The economic roadblocks in developing intranasal naloxone and/or switching its status from prescription-to-OTC are profitability and cost. As noted above, naloxone has been available as an OTC drug in Europe since the 1980's without any reported negative outcomes.[228] Naloxone is a post-patent generic drug[229] however, therefore, making an intranasal formulation or switching its status from prescription-to-OTC would require filing an NDA.[230] Thus, one may suspect that a current

[225] *See* SEGAL PRESENTATION, *supra* note 218, at 19, 23–24; *see also* FDA MEETING TRANSCRIPT, *supra* note 14, at 186–87.

[226] *See* SEGAL PRESENTATION, *supra* note 218, at 19, 25; *see also* FDA MEETING TRANSCRIPT, *supra* note 14, at 187–88.

[227] *See* FDA MEETING TRANSCRIPT, *supra* note 14, at 5 (The meeting was organized "collectively by the FDA, by the National Institute of Drug Abuse, by the Centers for Disease Control and Prevention, and by the Office of the Assistant Secretary for Health in the Department of Health and Human Services.").

[228] *See* Kim, *supra* note 142, at 403 n.15, 25 (citing Scott Burris et al., *Legal Aspects of Providing Naloxone to Heroin Users in the United States*, 12 INT'L J. DRUG POL'Y 237, 242 (2001); S. Galea, et al., *Provision of Naloxone to Injection Drug Users as an Overdose Prevention Strategy: Early Evidence from a Pilot Study in New York City*, 31ADDICTIVE BEHAVIORS 907 (2006)).

[229] *See* Beletsky, *supra* note 203, at 17.

[230] *See* FDA MEETING TRANSCRIPT, *supra* note 14, at 180–81.

manufacturer of naloxone would be the foremost advocate in developing intranasal naloxone and/or in seeking OTC approval.[231] Rather than advocating for an intranasal formulation or initiating OTC approval studies, however, several former manufacturers of naloxone including Wyeth, Baxter and Endo Pharmaceuticals have exited the market.[232] This suggests that the market and/or profitability of naloxone are "too small to justify the investment."[233]

Scholars have suggested that classifying an intranasal formulation of naloxone as an orphan drug may increase industry interest in entering the naloxone market.[234] The Orphan Drug Act[235] provides both economic incentives and regulatory support for drugs targeting a rare disease or condition. Pursuant to the Orphan Drug Act, a rare disease or condition is defined as any disease or condition that

> affects less than 200,000 persons in the United States, or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.[236]

Following orphan drug designation, public and private entities developing the orphan drug may receive grants from or enter into contracts with the FDA to defray the costs associated with preclinical and clinical testing.[237] In addition to defraying the cost associated with testing the drug, orphan drug designation allows the FDA to provide recommendations for the non-clinical and clinical testing necessary to facilitate FDA approval.[238] Further, orphan drug designation provides tax incentives[239] and increased

231 *See* Burris, *supra* note 13, at 333–34.

232 *See* Beletsky, *supra* note 203, at 17.

233 *See* Burris, *supra* note 13, at 333–34.

234 *Id.* at 337.

235 21 C.F.R. § 316 (providing "procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics.").

236 21 U.S.C. § 360bb(a)(2).

237 *See generally id.* at § 360ee(a) (giving the Secretary the authority to make grants to and enter into contracts with public and private entities and individuals to assist in defraying costs).

238 *Id.* at § 360aa(2).

239 26 U.S.C. § 45C (West, Westlaw through 2014).

market exclusivity[240] to the developer.

The impetus underlying the belief that intranasal naloxone may qualify as an orphan drug is the designation of suboxone as such.[241] Suboxone, a combination of buprenorphine and naloxone, received approval in 2002 for the treatment of opioid dependence.[242] Although suboxone was classified as an orphan drug, reports indicate that intranasal naloxone is not eligible for orphan drug designation[243] therefore mitigating industry interest in pursuing the development of an intranasal formulation.

An additional economic roadblock to expanding access to naloxone is the cost associated with developing an intranasal formulation or conducting the requisite studies to support a prescription-to-OTC switch. As noted above, intranasal naloxone has been determined to be not eligible for orphan drug designation.[244] Thus, the costs associated with developing the drug are ineligible to be defrayed by the federal government pursuant to the Orphan Drug Act.[245] Given the potential costs to support the regulatory requirements necessary for FDA approval, it is not surprising that Hospira,[246] the sole manufacturer of injectable naloxone, has yet to submit an NDA for the intranasal formulation or initiated studies required for switching naloxone's status from prescription-to-OTC.

Thus, stimulating industry interest in developing an intranasal formulation of naloxone and/or in switching its status from prescription-to-OTC to increase access to this medication

240 21 U.S.C. § 360cc (providing 7 years of market exclusivity following FDA approval to market an orphan drug).

241 *See Orphan Drug Designation and Approvals*, FDA.GOV, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=079093 (last visited Oct. 16, 2015) (listing suboxone as an orphan drug since Oct. 27, 1994); *see also* FDA MEETING TRANSCRIPT, *supra* note 14, at 201 (explaining that the closest example of giving naloxone nasally is in a paper that was a drug abuse liability study performed at the University of Kentucky by crushing suboxone tablets and letting subjects snort the suboxone power).

242 *Orphan Drug Designation and Approvals*, FDA.GOV, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=079093 (last visited Oct. 16, 2015) (listing that approval of suboxone for "treatment of opioid dependence" occurred on Oct. 8, 2002).

243 *See* Daniel P. Wermeling, *Considerations for Development and Marketing of Needleless Naloxone HCL Delivery Systems*, FDA.GOV (Apr. 12, 2012), http://www.fda.gov/downloads/Drugs/NewsEvents/UCM300876.pdf (presenting on "naloxone drug delivery product market" and stating that naloxone is not eligible for an orphan drug designation for this indication).

244 *Id.*

245 21 U.S.C. § 360ee (2012).

246 *See* Szalavitz, *supra* note 157.

requires action by the federal government. Requiring that naloxone be given to patients prescribed opioids as part of their pain management therapy may facilitate industry interest in creating alternative, easy-to-use formulations of the drug. The increased demand for naloxone in easy-to-use formulations would increase the profitability of the naloxone market for the pharmaceutical industry. Requiring that naloxone be given to patients receiving opioids for pain management may spark the interest of pharmaceutical companies that currently develop opioid analgesics and are able to capitalize on both the opioid analgesic and opioid overdose prevention markets.

Alternatively, the federal government may stimulate industry interest via federal funding to support the development of and clinical testing for alternate formulations of naloxone to meet the FDA recommendations noted above. The federal government has initiated such action by placing the development of alternate formulations of naloxone at the forefront of their research strategic plans. For example, in an effort to defray the costs associated with developing new formulations of naloxone and increase industry interest, the NIDA has provided approximately $4.5 million to AntiOp, Inc. for studies to support the development of intranasal naloxone.[247] AntiOp, Inc. is developing and testing a specially formulated naloxone solution for nasal delivery.[248] As the FDA has specified the final research requirements necessary for approval (including a determination that efficacy and toxicology studies are not required), AntiOp, Inc. anticipated that its intranasal naloxone formulation would be available within the following twelve to eighteen months.[249] In addition to providing support for AntiOp, Inc.'s intranasal naloxone formulation, the NIDA has also supported the initial clinical data generated from Lightlake Therapeutics' naloxone nasal spray.[250] Initial clinical data demonstrates that Lightlake

[247] *See Naloxone Nasal Spray on Development Fast Track as Emergency Treatment for Opioid Overdose*, BUSINESS WIRE (Sept. 20, 2013), http://www.businesswire.com/news/home/20130920005500/en/ (last visited Oct. 16, 2015).

[248] *Id.*

[249] *Id.*

[250] *See Initial Data from Lightlake Therapeutics Joint Clinical Trial with NIDA Shows Nasal Delivery of Naloxone for Opioid Overdose as a Promising Treatment,* PRNEWSWIRE (Dec. 3, 2013), http://www.prnewswire.com/news-releases/initial-data-from-lightlake-therapeutics-joint-clinical-trial-with-nida-shows-nasal-delivery-of-naloxone-for-opioid-overdose-as-a-promising-treatment-234288381.html (last visited Oct. 16, 2015).

Therapeutics' nasal spray can potentially deliver naloxone into the bloodstream as quickly as injectable naloxone.[251]

Thus, to increase access to naloxone and prevent opioid overdose fatalities, intervention by the federal government is required. By providing a comprehensive strategic plan to combat opioid overdose fatalities and funding to support the development of alternate naloxone formulations and/or studies required for naloxone to switch from a prescription to OTC drug, increased access to naloxone will be expedited.

XIII. CONCLUSION

Opioid overdose is a growing public health concern in the United States. In response to the increasing number of opioid overdose fatalities, several states have implemented opioid overdose response programs. Although critical to the prevention of opioid overdose related deaths by allowing naloxone to be prescribed to and administered by third-party administrators, access to naloxone is still limited as there are many states that have yet to implement these programs. Access to naloxone is also limited due its prescription status and the lack of industry interest in performing the necessary studies to develop alternate formulations of naloxone and/or switch naloxone from a prescription to an OTC drug. Federal intervention, including regulatory guidance and financial support, is required to stimulate industry interest in increasing access to this life-saving medication. Such intervention will expedite the development of alternate naloxone formulations and/or a switch from its current prescription to an OTC status as well as increase access to naloxone.

[251] *Id.*