4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-N-2673]

Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing our preliminary assessment that certain types of naloxone hydrochloride ("naloxone") drug products may be approvable as safe and effective for nonprescription use. It is our preliminary opinion at this time that naloxone nasal spray up to 4 milligrams (mg), and naloxone autoinjector for intramuscular (IM) or subcutaneous (SC) use up to 2 mg, have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner. We believe the prescription requirement for these naloxone products might not be necessary for the protection of the public health. However, we need additional data such as product-specific data on the nonprescription user interface design, including packaging and labeling, to make a conclusive determination in this respect. The Federal Food, Drug, and Cosmetic Act (FD&C Act) does not permit the simultaneous marketing of the same drug with the same active ingredient as both a prescription and nonprescription product, absent a clinically meaningful difference between them. Therefore, if and when FDA has sufficient data to support approval of a nonprescription naloxone product (e.g., through submission and approval of an application for a nonprescription naloxone product or a supplemental application to switch an FDA-approved naloxone product from prescription to nonprescription status), currently marketed naloxone products labeled as "Rx only" with no clinically meaningful difference from the approved nonprescription products will be considered misbranded.

DATES: Either electronic or written comments on the notice must be submitted by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2022-N-2673 for "Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18,

2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Ayako Sato, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6206, Silver Spring, MD 20993, 240-402-4191.

SUPPLEMENTARY INFORMATION:

I. Background

A. FDA's Current Regulatory Framework

Two regulatory pathways to bring a nonprescription drug product to market in the United States are: (1) the over-the-counter (OTC) drug review process under section 505G of the FD&C Act (21 U.S.C. 355h) with respect to OTC monograph drugs and (2) the application process under section 505 of the FD&C Act (21 U.S.C. 355) or, for a biological product, under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

Under the OTC drug review process, a nonprescription drug product may be marketed without an application approved under section 505 of the FD&C Act if the nonprescription drug product meets the requirements of section 505G of the FD&C Act, and other applicable requirements. In addition, FDA approves drugs under section 505 of the FD&C Act and, for biological products, under section 351 of the PHS Act, as either prescription or nonprescription drug products.

An applicant may submit a new drug application (NDA) for a nonprescription drug product using the pathways described in section 505(b)(1) or (2) of the FD&C Act to market a

new drug product. A section 505(b)(1) NDA includes full reports of investigations to demonstrate that the proposed drug product is safe and effective under the conditions prescribed, recommended, or suggested in its proposed labeling (see sections 505(d) and (b)(1) of the FD&C Act). An NDA submitted pursuant to section 505(b)(2) of the FD&C Act also includes information to demonstrate that the proposed drug product is safe and effective under the conditions prescribed, recommended, or suggested in its proposed labeling, but at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. An NDA for a nonprescription drug product must include, among other things, information to demonstrate that consumers can appropriately self-select[1] the proposed drug product and use the drug product safely and effectively without the supervision of a healthcare practitioner.

Applicants may submit an abbreviated new drug application (ANDA) using the pathway described in section 505(j) of the FD&C Act for a drug product that is a generic version of a previously approved drug product (typically an approved brand-name drug). An ANDA for a nonprescription drug product generally references a nonprescription drug product previously approved under section 505(c) of the FD&C Act (known as the reference listed drug ("RLD")) and relies on the Agency's finding that the RLD is safe and effective. An ANDA generally must contain information to show that the proposed generic product: (1) is the same as the RLD with respect to the active ingredient(s), route of administration, dosage form, strength, labeling (with certain permissible differences) and (2) is bioequivalent to the RLD. The procedures and requirements for the submission and approval of NDAs, ANDAs, and supplements to those applications are set forth in 21 CFR part 314.

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[1] E.g., 21 CFR 201.5. Because nonprescription drugs are available to consumers without the supervision of a healthcare provider, nonprescription labeling must on its own be able to effectively communicate to a general consumer the information required for the safe and effective use of the product. Therefore, "self-select" means that a consumer can apply the label information to their personal medical situation and make correct decisions about whether it is appropriate for them to use or not use the drug product. In some cases, nonprescription products may be selected and purchased by someone else, such as a family member or caregiver and administered to another family member or individual, such as to a child or elderly person.

Section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)) requires that certain drug products be dispensed only upon prescription of a practitioner licensed to administer such drug product. The prescription requirement applies to any drug product which: (1) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to dispense such drug product or (2) is limited by an approved application under section 505 of the FD&C Act to use under the professional supervision of a practitioner licensed by law to administer such drug product. If the approved drug product does not meet the criteria for prescription-only dispensing, it may be marketed as nonprescription, provided other applicable requirements are met.

Under section 503(b)(4)(A) of the FD&C Act, the label of a drug product that is subject to the prescription dispensing provisions of section 503(b)(1) (i.e., a prescription drug product) must bear, at a minimum, the "Rx only" symbol, or else it is misbranded. Section 503(b)(4)(B) of the FD&C Act provides that a drug product to which the prescription provisions of the FD&C Act do not apply (i.e., a nonprescription drug product) will be deemed to be misbranded if at any time before dispensing, the label of the drug product bears the "Rx only" symbol. FDA has interpreted the language in section 503(b)(4) of the FD&C Act to allow simultaneous marketing of drug products with the same active ingredient as prescription in one case and nonprescription in another if some clinically meaningful difference, such as a difference in indication, strength, route of administration, dosage form, or patient population, exists between the drug products that makes the prescription product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer the drug product (see 83 FR 13994, April 2, 2018; see also 70 FR 52050, September 1, 2005). This effectively means that, absent a clinically meaningful difference between the products that makes the prescription product safe and effective only under the supervision of a licensed healthcare practitioner, simultaneous marketing

of two drug products with the same active ingredient as, respectively, a prescription and a nonprescription drug product, would result in the prescription drug product being misbranded.

Although the OTC drug review process under section 505G of the FD&C Act and the application process under section 505 of the FD&C Act or, for a biological product regulated as a drug, under section 351 of the PHS Act, are the primary ways in which an applicant brings a nonprescription drug product to market, a drug originally approved as a prescription drug may be switched to nonprescription status if FDA finds that prescription requirement for such drug is not necessary for the protection of the public health.[2] For a drug product to switch from prescription to nonprescription status, FDA must also determine there are sufficient data demonstrating that the drug product can be used safely and effectively by consumers without the supervision of a licensed healthcare practitioner.[3]

As discussed below, such information may include evidence from a range of studies (e.g., label comprehension study, human factors study, and/or actual use study). Usually, manufacturers seeking authorization to market such a prescription product as nonprescription are responsible for conducting these studies to show that their product can be used safely and effectively without the supervision of a healthcare practitioner. Generally, manufacturers of nonprescription drug products must also label and package their products such that the consumer can use the drug product safely for the purposes for which it is intended. This includes complying with applicable labeling requirements under 21 CFR part 201, including the format and content requirements for nonprescription drug product labeling under § 201.66 (21 CFR 201.66). Labeling created to satisfy the requirements in § 201.66 is commonly referred to as the Drug Facts labeling (DFL). The DFL is intended to enable consumers to self-select appropriately and use the nonprescription drug product safely and effectively. In addition to the

[2] See 21 CFR 310.200(b).
[3] Id.

DFL, for a nonprescription drug product that requires an approved application under section 505, FDA may approve additional labeling to help ensure safe and appropriate use.

B. Naloxone

1. General Background on Naloxone

The opioid crisis, which encompasses misuse, abuse, and overdose deaths involving illicit and prescription opioids, was declared a public health emergency (Opioid PHE) in 2017 (Ref. 1). Since 2017, the Opioid PHE declaration has been renewed multiple times. More than 80,000 people died of opioid-involved overdose deaths in the 12-month period ending in January 2022, representing 75 percent of all drug overdose deaths. The number of opioid-involved overdose deaths increased from 71,000 deaths in the preceding year (Ref. 2).[4]

Naloxone is a critical tool to help reduce opioid overdose deaths and address this public health crisis. Opioid overdose is characterized by life threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality. Naloxone is a nonselective opioid receptor antagonist that reverses the effects of respiratory depression and sedation by displacing opioids from the mu-opioid receptor in the CNS. Timely administration of naloxone, usually within minutes of the first signs of an opioid overdose, can counter the overdose effects.

a. Approval history for prescription naloxone products. There are currently no naloxone products approved by FDA for nonprescription use. Naloxone is available as a prescription drug in several strengths, dosage forms, and routes of administration. It was first approved in the United States in 1971 with the tradename NARCAN. NARCAN, as originally approved, was an injectable naloxone product that could be delivered via the intravenous (IV), IM, or SC routes of administration, and was available in vials or ampules.[5] It was widely used by both hospital and first responder personnel. As opioid use and overdoses increased, naloxone was increasingly

[4] Among deaths with drug overdose as the underlying cause, using predicted provisional number of deaths for opioids (ICD-10 multiple cause-of-death codes for illicit and prescription opioids: T40.0-T40.4, T40.6).
[5] NARCAN (naloxone hydrochloride) injection (NDA 016636) for IV, IM, SC use has been discontinued. However, generic naloxone hydrochloride injection products continue to be marketed.

used by non-healthcare professionals. Multiple initiatives across the United States provided naloxone and instructions for its use to populations at risk of opioid overdose and their family, friends and/or caregivers. These programs were effective at getting naloxone into the hands of those who might witness an overdose (see section C of this document). However, because the injectable naloxone products at the time were only available in glass vials and ampules, they needed to be distributed with syringes and needles for manual injection, or with syringes and atomizers for nasal administration. These products required additional preparation or assembly before administration and were sometimes packaged as improvised naloxone kits. Hence, there was a public health need for naloxone products that did not require additional preparation or assembly before administration and could be administered quickly and safely by a layperson.

In 2014, FDA approved EVZIO, a 0.4 milligram (mg) prefilled, single-use auto-injector naloxone drug product for IM or SC use, followed shortly thereafter by FDA approval of NARCAN, a 4 mg, prefilled, single-dose nasal spray in 2015. More recently, two higher dose[6] naloxone products were approved: KLOXXADO, an 8 mg, prefilled, single-dose nasal spray, approved on April 29, 2021, and ZIMHI, a 5 mg single-dose, prefilled syringe with an integrated needle for IM or SC use, approved October 15, 2021. These prescription naloxone products do not need additional supplies or additional assembly prior to use (e.g., the drug product is already prefilled in the device for administration), and they represent an effort to develop and market products that could potentially be administered by individuals without medical training (i.e., laypersons) in community settings (i.e., "community-use" naloxone products) in the interest of public health.

b. Approval standard for prescription naloxone products[7]. Applicants proposing novel naloxone products (including nonprescription naloxone products) need to demonstrate sufficient

[6] For this notice, "higher dose" naloxone products refer to products with dosage strengths above 4 mg for IM naloxone products and above 2 mg for IM/SC/IV.

[7] The approval standard for prescription naloxone products as described in this section was discussed extensively at the October 5, 2016, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. See website at https://wayback.archive-

systemic absorption of naloxone as well as rapidity of onset compared to an approved naloxone product, particularly in the early critical period after drug administration. This is in addition to any other studies needed to support approval of the product (e.g., human factors study).

FDA has determined that it is not necessary for applicants to conduct clinical efficacy trials with novel naloxone products, as effective doses have already been established (Ref. 3). Clinical efficacy trials present significant logistical and ethical challenges, as approved naloxone products are already available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. Therefore, historically, efficacy has been based on information known about other naloxone products and supported by a relative bioavailability study conducted in healthy volunteers. In addition to the bioavailability studies conducted by applicants to support their proposed naloxone doses/products, applicants may also need to provide additional data, such as literature reviews, to support the safety and effectiveness of their products if the exposure is different. As newer products with higher doses and/or exposures have been proposed, the importance of such literature support has increased.

c. Layperson use of naloxone: "community-use" naloxone products and improvised naloxone kits. Since 2014, FDA has approved several prescription naloxone drug-device combination products for the emergency treatment of a known or suspected opioid overdose, including EVZIO, NARCAN, KLOXXADO, and ZIMHI. These specific FDA-approved prescription products are referred to in this notice as "community-use" naloxone products. "Community-use" products are specifically designed to facilitate use by laypersons, without the need for additional supplies or assembly before use. Because "community-use" naloxone products, such as prefilled auto-injectors (Ref. 9), nasal sprays (Ref. 10), and syringes with an integrated needle presentation, do not require other medical supplies prior to administration, safe and effective use by laypersons in the community may be facilitated. In addition, as part of the

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it.org/7993/20170111202120/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm.

approval process, data were required to demonstrate that these "community use" naloxone products administered using the integrated device can achieve naloxone blood levels appropriate to reverse an opioid overdose.

In addition to "community-use" naloxone products, other naloxone formulations may be used by laypersons in community settings (e.g., naloxone in vial, ampule, and some prefilled syringe presentations). However, these products were not specifically designed to be used in the community setting. Nevertheless, it is important to emphasize that all FDA-approved prescription naloxone products, regardless of whether they were specifically designed to be "community-use" naloxone products, may be considered options for community distribution to laypersons for use outside of the healthcare setting (Ref. 4).[8]

Because some naloxone products in vial, ampule, and some prefilled syringe presentations may require other medical supplies and additional preparation prior to administration (e.g., transfer to a syringe, measurement of a specific dose, attachment to an atomizer or needle, etc.), there may be added complexity to administration of the products and increased risk for medication errors when used by laypersons. When distributed by community-based naloxone distribution programs, for example, additional items are often packaged along with the naloxone in improvised naloxone kits, and these kits may contain a syringe, needle, or atomizer, as well as, but not limited to, alcohol pads, bag valve masks, rubber gloves, and instructional or educational materials on naloxone use and overdose prevention (Ref. 5). Even with these additional materials, these improvised naloxone kits may be difficult for some laypersons to use, and there are reports of administration and dosing errors associated with laypersons using improvised naloxone kits (Refs. 6 to 8). In addition, the blood levels of naloxone achieved with administration using various improvised naloxone kits may not be known (see Ref. 11).

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[8] FDA has previously stated that all FDA-approved naloxone products "may be considered as options for community distribution and use by individuals with or without medical training to stop or reverse the effects of an opioid overdose" (Ref. 4).

d. Recent naloxone sales and prescription data. Since the introduction of "community-use" naloxone products EVZIO, NARCAN, KLOXXADO, and ZIMHI to the market, the opioid epidemic has evolved and naloxone use has increased. Based on FDA's analyses using proprietary databases, nationally estimated sales[9] and dispensed prescriptions[10] for naloxone products increased across all healthcare settings from 2017 to 2021, largely due to a substantial increase in naloxone nasal spray distribution. The estimated number of naloxone units sold increased by 81 percent from approximately 5.1 million units in 2017 to approximately 9.3 million units in 2021. Injectable and nasal spray sales to hospitals increased by more than 50 percent, and sales to retail pharmacies tripled during this time period. In 2017, approximately half of naloxone sales to retail pharmacies were for the nasal spray, and by 2021 over 90 percent of sales were for the nasal spray. The volume of naloxone products sold to other healthcare settings (e.g., to clinics or in prisons and universities) also increased. Similar to sales to healthcare settings, the estimated number of naloxone prescriptions dispensed from pharmacies increased from under half a million prescriptions in 2017 to 1.5 million prescriptions in 2021. In 2021, over 95 percent of naloxone prescriptions dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies were for the nasal spray.

It is important to note that the proprietary databases used for these analyses underestimate total availability and distribution of naloxone products in the United States because donations from manufacturers and most direct sales to community-based naloxone distribution programs are not well represented in the data above. These donations and direct sales may be a substantial source of naloxone to individuals with opioid use. Some sources cite that community-based naloxone distribution programs received over 2 million injectable naloxone doses donated by manufacturers or purchased in bulk at low cost between 2017 and 2021 (Refs. 12 and 13). While the analyses showed a decrease in injectable naloxone dispensed from retail pharmacies from

[9] IQVIA. National Sales Perspectives™. Data extracted January 2022. Sales were measured in volume of "units" sold, representing the number of vials, auto-injectors, nasal sprays, and syringes.
[10] Symphony Health. Metys™. Data extracted January 2022.

2017 to 2021, distribution patterns by product formulation from community-based naloxone distribution programs may differ from the FDA analyses using data from proprietary databases. Furthermore, some naloxone sold to hospitals may also be distributed to settings such as outpatient clinics and emergency medical services (EMS). Although the analyses show an increased number of prescriptions dispensed from retail pharmacies and an overall increase in naloxone sales over the past 5 years, the increases in overdose deaths reflect a need for increased access and availability of naloxone products particularly for non-healthcare settings.

2. Benefit-Risk Considerations for Naloxone Products

FDA-approved prescription naloxone products have a favorable benefit-risk profile. Naloxone is not a controlled substance and has no known abuse potential. Naloxone is a potentially life-saving treatment when used together with other appropriate measures (e.g., calling 911).[11] Current evidence suggests that increasing access to naloxone has the potential to reduce opioid overdose deaths. Results from multiple observational studies show that naloxone distribution and overdose education targeted to populations likely to observe an overdose is an effective intervention strategy (Refs. 14 to 17). For example, studies of community-based overdose education and naloxone distribution programs report high rates of successful opioid overdose reversal attempts, reflecting numerous lives saved (Refs. 15 and 16). Similarly, results from modeling efforts (Refs. 18 to 21) suggest that increased distribution and use of naloxone could contribute to a decrease in overall deaths related to opioid overdose. A systems modeling study funded by FDA estimates that nearly 20,000 deaths were averted due to layperson naloxone administration from 1999 to 2020, particularly in more recent years (Ref. 20). This modeling research also projects that increasing naloxone distribution (beyond EMS providers) would have among the largest and most immediate future effects on reducing opioid overdose deaths among 11 broad strategies tested (Ref. 21). Although there are important limitations to

[11] It is imperative that individuals administering naloxone call 911 for prompt assistance. Naloxone is a temporary treatment, so repeat doses may be required. Management options for overdose or any naloxone adverse events may be different in non-healthcare settings (e.g., verbal deescalation, rescue breathing, chest compressions) than they are in healthcare settings (e.g., medications for specific adverse events, supplemental oxygen, cardiac defibrillator).

each study, results consistently show overall lives saved with increased naloxone distribution and use, especially when distributed to those most likely to observe an opioid overdose.

As with all drugs, the risks associated with naloxone use also need to be considered. It is well-known that among patients with physical dependence to opioids, naloxone use may result in acute-onset, precipitated opioid withdrawal (precipitated withdrawal),[12] referred to in the labeling for currently marketed naloxone products as "Precipitation of Severe Opioid Withdrawal" (Refs. 22 to 25). As noted in the labeling for currently approved naloxone products, naloxone-induced precipitated withdrawal may also be associated with other clinically serious adverse events such as pulmonary edema, cardiac arrythmias, and agitation--these and other adverse events are labeled in the context of postoperative opioid reversal (Refs. 22 to 25) but could also occur among opioid-dependent populations (Refs. 24 to 28). The incidence of such naloxone-induced adverse events in the community setting may be influenced by factors such as naloxone dose, underlying patient comorbidities, and concomitant medications or co-exposures, including intentional or unintentional polysubstance use. In situations involving multiple substance exposure, naloxone use may result in unmasking the effects of non-opioid substance(s), such as other sedating drugs or stimulants (Refs. 29 and 30). The rise in intentional polysubstance use and unintentional exposure to contamination in the illicit drug supply (Ref. 31) make reversing overdoses in the current environment more complex than in previous times. Furthermore, respiratory and CNS depression may recur after the first dose of naloxone because of the difference in duration of action between naloxone and the opioid. Hence, it is highly important that users of naloxone products activate emergency medical services.

Despite these potential risks, the benefit of broader use of naloxone in reversing potentially fatal events is significant, even as surveillance for and mitigation of risks are

[12] Precipitated withdrawal, resulting from administration of an opioid antagonist, should be considered mechanistically and clinically distinct from withdrawal resulting from cessation, or significant reduction in opioid use. In an adult opioid-dependent person, precipitated withdrawal would be expected to result in more rapid onset signs and symptoms of greater severity, while withdrawal resulting from cessation would be expected to occur more gradually, with symptoms that, while uncomfortable, may not necessarily require urgent medical attention.

important. We believe that the public health impacts associated with a serious adverse reaction to naloxone, as concerning as they may be, are still far less than the public health impacts of opioid overdose death. The public health benefits of FDA-approved prescription naloxone products in preventing overdose deaths clearly outweigh potential serious adverse reactions associated with naloxone administration.

As we consider how the favorable benefit-risk profile for prescription naloxone products may translate to nonprescription naloxone products, FDA will need to ensure that products developed for nonprescription use are appropriately designed to support intended users' needs for their intended use in intended environments without the supervision of a healthcare practitioner.

Additionally, we would encourage community programs and other stakeholders to offer training to help further reduce the risks described above with administration of naloxone to further benefit the public health. Such programs could communicate critical information and educate on topics such as:

- Prompt activation of EMS (e.g., calling 911)
- Opioid overdose recognition
- Alternate etiologies of unresponsiveness
- Respiratory support prior to naloxone administration and onset if naloxone is not immediately available
- Naloxone administration
- Awareness of possible adverse events related to naloxone administration
- Dose titration to the lowest effective dose for appropriate clinical endpoints
- Appropriate interventions supplemental to naloxone administration (e.g., physical stimulus, positioning, rescue breathing, chest compressions, defibrillation)

3. FDA's Efforts to Increase Naloxone Availability and Accessibility

In light of the important role that naloxone can play in reversing opioid overdose, FDA is committed to increasing access and broadening distribution of naloxone products as one strategy to help address the current opioid overdose crisis. Over the last several years, FDA has taken a number of steps to improve availability of naloxone products, including: encouraging manufacturers to pursue development of nonprescription naloxone products; requiring drug manufacturers for all opioid pain relievers and medicines to treat opioid use disorder to add new recommendations about naloxone to the prescribing information of their respective opioid products; approving new naloxone products, including generics; approving the extension of the shelf life of naloxone nasal spray from 24 months to 36 months; and issuing an immediately-in-effect guidance to industry clarifying the scope of the public health emergency exclusion and exemption under the Drug Supply Chain Security Act as they apply to the distribution of FDA-approved naloxone products.

FDA has also held public meetings to solicit scientific and regulatory input on naloxone. On October 5, 2016, the Agency held a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss what is known about the safety of using naloxone and the risk of precipitating an acute opioid withdrawal syndrome, issues specific to dosing in pediatric patients, the clinical pharmacology of naloxone, and information about the use of naloxone.[13] We asked the advisory committee members for advice on whether the pharmacokinetic standard for the approval of naloxone products based on a demonstration of comparable or greater naloxone levels compared to 0.4 mg of naloxone given intramuscularly is sufficient, and if higher doses are recommended, how to weigh the need for effectiveness against the risk of precipitating an acute withdrawal syndrome. The Agency also sought feedback about naloxone dosing for pediatric patients as

[13] Meeting materials are available on the FDA website at https://wayback.archive-it.org/7993/20170111202120/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm.

well as whether there is benefit in having different doses for the same or different products and how a clinician can determine which product to prescribe.

On December 17 and 18, 2018, the Agency also held a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee (December 2018 AC Meeting) to discuss ways in which the Agency could increase the availability of naloxone products intended for use outside of the healthcare setting (see Ref. 3). The topic of nonprescription naloxone was also discussed at this meeting, and participants suggested switching prescription naloxone to nonprescription status. Some participants stated that FDA approval of a nonprescription naloxone product would increase access to and availability of naloxone. Others commented that having naloxone available as a nonprescription product and on store shelves would help increase naloxone use because it would overcome the stigma associated with opioid use and the need for interaction with a pharmacist to obtain prescription naloxone for possible opioid overdoses. Others added that even though some States have naloxone access laws that would allow an individual to obtain naloxone without a patient-specific prescription, these State laws have not significantly expanded access to naloxone in the same way that nonprescription naloxone might. A few participants also noted that eliminating the prescription status for naloxone could make it easier to purchase naloxone in bulk and reduce legal and non-legal barriers that exist for distribution programs that require third-party prescribing.

Although the meeting was specifically focused on increasing naloxone availability, pricing and cost concerns over naloxone products were voiced by several commentors. We heard from the public that the retail price of the currently approved naloxone products can be high. Others expressed concern regarding insurance coverage for naloxone products if such products were switched from prescription to nonprescription status.

Echoing some of the comments provided about barriers to naloxone availability and access during the December 2018 AC Meeting, common barriers reported in a limited review of

published studies included fear of stigma and discrimination when obtaining naloxone from physicians or pharmacists and cost (Refs. 32 and 33). Studies report participants' past negative experiences at a pharmacy impacting confidence for obtaining naloxone through a pharmacy (Ref. 33) and a feeling of judgment by doctors toward people who use drugs nonmedically (Ref. 32). Studies identified that naloxone nasal spray had high costs, pharmacies did not have naloxone in stock, and, despite State naloxone access laws, naloxone was unavailable without a patient-specific prescription (Refs. 34 to 36).

4. FDA's Efforts to Facilitate Development of Nonprescription Naloxone

In the face of the increasing incidence of opioid overdose in the United States and in an effort to increase potential naloxone availability in the community, FDA developed an innovative strategy to accelerate development of potential nonprescription naloxone products. Sponsors interested in bringing a naloxone drug product to market via a nonprescription development pathway had cited the development of a nonprescription drug label as a major barrier in bringing their products to market. Thus, FDA took the unprecedented steps of developing a model naloxone DFL and assessing consumers' ability to understand it.

Drugs that do not contain adequate directions for safe and effective use are considered misbranded.[14] "Adequate directions for use" means directions under which a layperson can use a drug safely and effectively and for the purposes for which it is intended.[15] Prescription drugs, by definition, cannot bear adequate directions for use by a layperson; FDA regulations provide an exemption from the requirement to bear adequate directions for use by a layperson for FDA-approved prescription drugs that bear their FDA-approved labeling.[16] For prescription products, the prescribing information is written for healthcare professionals. It must include all information necessary for a healthcare professional to evaluate the appropriateness of the drug for a particular patient. For nonprescription products, the labeling needs to be adequately

[14] 21 U.S.C. 352(f)(1).
[15] 21 CFR 201.5.
[16] 21 CFR 201.100 and 201.115.

understood by the general public, regardless of prior experience with the drug in question and across a broad range of literacy, including those with limited literacy.[17] Nonprescription drug label development may be time and resource intensive and requires: (1) identifying the essential elements of the prescribing information, which are necessary for the proper and safe use of the medication; (2) using these elements to create a consumer friendly DFL; and (3) verifying with extensive consumer testing that consumers can comprehend the DFL and use the product appropriately without the help of a healthcare professional.

As mentioned above and as previously communicated in a 2019 *Federal Register* notice (84 FR 8728), FDA has taken the unprecedented step of designing and assessing comprehension of two versions of a model naloxone DFL for use by industry to support a nonprescription drug application (Ref. 37). Future sponsors of nonprescription naloxone products using the model DFL without changes to the previously tested portions may avoid performing a comprehensive Label Comprehension Study (LCS) for the portions previously tested. Required testing would be limited to any minor modifications of the DFL and the information necessary to evaluate device-specific information (such as how to use a particular injector or spray device).

As a foundation for creating the model naloxone DFL, FDA used the prescribing information for the two prescription products that had been designed for "community use" as of 2016: (1) EVZIO, a prefilled auto-injector and (2) NARCAN, an intranasal spray. FDA clinicians, in consultation with experts on the treatment of addiction, distilled the prescribing information for naloxone into what were deemed to be the critical elements in instructions for emergency use. They took the relatively lengthy prescription labeling and condensed it to fit the succinct content and format of a nonprescription DFL.

An independent research contractor conducted qualitative testing of small segments of the DFL comprising indepth, sequential, one-on-one interviews of 36 subjects to determine the clearest and simplest presentation of important consumer information. This was followed by

[17] See, e.g., 21 U.S.C. 352(c).

pilot testing the revised label in another 36 subjects. Enhancement of the label to improve readability included adding white space, boldface type, and "chunking" the information (i.e., breaking up information into small units that make it easier to notice). Additionally, pictograms were incorporated adjacent to the written text to clarify the stepwise directions.

The finalized version of the model DFL was tested in a pivotal LCS. The prespecified research design of the pivotal study included structured interviews in over 700 participants (including 33 percent with limited literacy, as defined by a score of 60 or less on the REALM (Rapid Estimate of Adult Literacy in Medicine)) across a wide range of potential nonprescription naloxone users. These participants included three groups: (1) those who had recently used opioids and their family and friends; (2) the general adult population not screened for opioid use; and (3) an adolescent population not screened for opioid use. Comprehension was tested by making sure that participants could answer open-ended questions to apply their understanding of the following elements or "critical tasks" necessary for safe use: (1) how to identify a person who might have an opioid overdose; (2) call 911; (3) stay with the person until 911 personnel arrive; and (4) recognize the signs of possible naloxone side effects that are to be expected. An FDA review team that was not involved in the design or conduct of the study reviewed the study report and determined that the model DFL comprehension results were adequate for all groups including those with limited literacy.

If applicants elect to use the model naloxone DFL created by FDA, the main piece of the DFL that would still need to be tested by the applicant are the device-specific instructions. The device-specific instructions may be added to the model DFL and evaluated in a simulated Human Factors (HF) validation study designed to evaluate whether the user interface can be used safely and effectively by intended users for the intended use under expected environment(s) of use. The HF validation study focuses on the collection of qualitative data and generally requires far fewer test participants as compared to a pivotal LCS, which is statistically powered. An applicant who starts with the FDA model naloxone DFL should only make changes to the DFL

that are related to device-specific instructions. Assuming that the DFL has not been altered in a substantial fashion, applicants then test just those added device-specific instructions in a simulated HF validation study, and if successful, have the opportunity to shorten the time of development of a potential nonprescription naloxone product. It is important to note that LCS and HF studies address, among other things, labeling and consumer behavior testing requirements; however, an applicant would still need to submit other data (e.g., bioavailability, stability, reliability of drug-device combination, non-clinical, justification for treatment of pediatric population, etc.) to support an application for a nonprescription product.

5. Other Considerations for Nonprescription Naloxone

The Agency is aware of concerns that are not directly related to the safe and effective use of nonprescription naloxone products, such as potential consequences of switching naloxone from prescription to nonprescription status, which have been raised by the public in multiple venues.

It is unclear how a switch to nonprescription naloxone would affect the distribution and supply of naloxone. One study published in 2019 estimates that naloxone pharmacy purchases could increase by 15 to 179 percent with a prescription-to-nonprescription switch of naloxone based on prior experience with nonprescription switches for nicotine gums and patches (Ref. 38). During the December 2018 AC Meeting, committee members discussed that drug shortages may be a problem and that capacity will need to be expanded dramatically to meet the needs of any expansion in naloxone distribution.

The committees also noted that if changes to the market were made, consideration should be given to ensure those who need naloxone are still able to get the drug at a reasonable cost. For example, the committees recommended that FDA ensure that a switch to nonprescription naloxone will not divert supplies away from community-based naloxone distribution programs and hospitals to settings where patients may be at less risk for experiencing an opioid overdose. Further, it is possible that even if the Agency could determine that certain naloxone products

would be safe and effective for nonprescription use, which would require all manufacturers of such products to switch their products from prescription to nonprescription absent a clinically meaningful difference, a firm may opt to stop marketing its product altogether rather than make the nonprescription switch, which could potentially contribute to a drug shortage.

We recognize that these concerns, although they may be outside of the Agency's drug approval considerations, may have significant impacts on naloxone availability and accessibility, and we will continue to work with our Federal partners to address them. We welcome comments from the public on any potential consequences of a switch from prescription to nonprescription status for naloxone products, which we will consider to the extent they may be address within our current authorities.

C. Factors Indicating That the Prescription Requirements for Certain Naloxone Products May Not Be Necessary

At this time, we believe that the prescription requirements for certain naloxone products may not be necessary for the protection of the public health, and we believe that these naloxone products have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner.

Naloxone, as a prescription product, has been used for many years (since 1971) to treat opioid overdose and has a favorable benefit-risk profile. The benefit-risk profile for naloxone takes into account naloxone's effectiveness in helping to reduce opioid overdose deaths. Timely administration of naloxone, usually within minutes of the first signs of an opioid overdose, can counter the overdose effects. Although naloxone administration is not without risks, as discussed above, the risks associated with opioid overdose and overdose-related deaths pose an even greater public health concern.

Moreover, community-based naloxone distribution programs have been providing naloxone to populations at risk of overdose without patient-specific prescriptions. These programs have provided naloxone to people who are likely to witness an opioid overdose and use

naloxone (Refs. 15 and 16). In addition, these programs may also provide overdose education or other support for appropriate use of naloxone. Some examples of community-based naloxone distribution programs are the Drug Overdose and Prevention Education (DOPE) program and the Massachusetts Overdose Education and Naloxone Distribution program. The DOPE program in San Francisco distributed 2,500 improvised naloxone kits to participants from 2010 to 2013. Of the 702 overdose reversal attempts reported to the DOPE program, over 95 percent were known to have survived (Ref. 16). In Massachusetts from 2006 to 2010, approximately 4,900 participants received improvised naloxone kits with mucosal atomization devices, and among those reporting use of the naloxone and the outcomes (n=359), 97 percent reported successfully reversing the overdose (Ref. 15). The high percentage of successful reversals in both programs should be interpreted cautiously as they represent reports from a select population reporting back to the program. Targeted naloxone distribution programs, such as distribution to those in opioid treatment programs, have been also shown to be effective methods of distribution (Refs. 39 to 45). Data are less clear on the effectiveness of a "universal precaution" approach whereby all patients prescribed opioid analgesics are also prescribed naloxone (Ref. 46).

Naloxone access laws (NAL) provide additional information on the distribution of naloxone to end-users without a patient-specific prescription. As of 2020, all 50 states and the District of Columbia have some form of NAL (Ref. 47). These laws are intended to increase naloxone availability for use in individuals experiencing an opioid overdose. With a prescription drug, a pharmacist would generally dispense the drug pursuant to a patient-specific prescription. However, naloxone differs from other prescription drugs due in part to its approved indication. As an emergency treatment for the reversal of overdose, naloxone may not necessarily be dispensed to the patient who experiences an overdose or administered by the patient who receives the prescription. Because naloxone may be acquired without a patient-specific prescription and may be administered to someone other than the person for whom the naloxone was dispensed, naloxone faces some challenges that may inadvertently hinder wider access to the

drug. For example, prescribers may be hesitant to prescribe naloxone to a third party for fear of liability (Ref. 48). NALs are meant to address these challenges by facilitating naloxone access outside of the traditional prescriber-patient relationship.

NALs vary from State to State and have changed over time, but generally, many have one or more of the following features: third-party provisions that allow a prescriber to prescribe naloxone to someone not directly at risk of overdose (e.g., caregiver, family member); standing order provisions that allow for non-patient specific prescriptions; and civil and/or criminal immunity provisions for prescribers and dispensers (Ref. 49). Studies have reported that NALs are associated with favorable public health outcomes (Ref. 13). These studies have reported increased distribution of naloxone, reductions in overdose deaths, and positive outcomes for emergency department events involving opioid overdose (Ref. 49). Naloxone obtained without a patient-specific prescription, as a result of NALs, has been administered by laypersons with little or no professional training and with evidence of some effectiveness at reversing opioid overdose (Refs. 15 to 17 and 50).

Notwithstanding these positive findings, barriers to access (e.g., stigma associated with illicit drug use) continue to persist despite NALs (Ref. 51). For example, based on a preliminary review, knowledge gaps regarding the details of State NALs may be contributing to pharmacies not making naloxone available for dispensing (Refs. 52 to 54). Specifically, some pharmacy staff working in pharmacies participating in State standing order programs did not fully understand the requirements under their State NAL and incorrectly stated that a patient-specific prescription or identification was required to obtain naloxone or that third parties (i.e., individuals other than the person at risk of an opioid overdose) could not obtain naloxone (Refs. 52 to 54). In California, although significant improvement to naloxone access has been achieved since the State's NAL first went into effect, naloxone continues to not be dispensed due to knowledge gaps regarding the State NAL (Ref. 54). The number of pharmacies reporting that they were willing to dispense naloxone without a patient-specific prescription increased by 80

percent from 2018 to 2020 (Ref. 54). However, fewer than half of all pharmacies interviewed were still willing to dispense naloxone without a patient-specific prescription, which indicates that improvements to access could still be realized (Ref. 54). A nonprescription naloxone option may provide another means to further increase naloxone availability (Ref. 54).

In summary, these models (i.e., community-based naloxone distribution programs and NALs) help to inform the potential public health benefit of nonprescription naloxone use by laypersons and have factored into our initial assessment that naloxone may be used safely and effectively for nonprescription use. The current availability of naloxone without a patient-specific prescription represents some useful general information that a naloxone product could potentially be used safely and effectively on a nonprescription basis.

Despite the useful information obtained through these models, they do not necessarily inform us on whether a layperson could, on their own, safely and effectively administer such product to a person experiencing an overdose without the supervision of a licensed practitioner and relying on the DFL. This is because, as mentioned above, improvised naloxone kits that are distributed by community-based naloxone distribution programs may include other items that accompany the drug (e.g., atomizer, instructions for safe use), and those distributing these improvised naloxone kits directly to the end user may be providing additional counseling on safe naloxone use. We are also aware that some State NALs require pharmacists to provide patient counseling before dispensing naloxone, which may include further information on naloxone safety, risks of opioid overdose, and resources on substance use disorder. We do not know to what extent these factors contribute to the safe and effective use of naloxone without the intervention of a learned intermediary, which may occur if a layperson obtains naloxone through one of these methods.

Moreover, even if such products are accompanied by educational or other materials to facilitate use, naloxone products distributed and dispensed through these models may be more challenging to administer (e.g., requiring assembly). Thus, in order to provide a meaningful

expansion in naloxone availability, an FDA-approved nonprescription naloxone product would need to be supported by LCS and HF studies and other data. Additionally, as described above, challenges associated with naloxone distributed through community-based naloxone distribution programs and naloxone acquired through NALs persist and providing another naloxone option--nonprescription naloxone products--with clear and understandable DFL instructions and not hampered by the patient-prescription requirements, may provide important value in addressing opioid overdoses.

D. Scope of the Notice

As discussed in section C of this document, we believe that certain naloxone products have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner. However, more direct, specific data would be needed to support a formal Agency determination that any particular form of naloxone (e.g., 4 mg naloxone nasal spray) is safe and effective as a nonprescription drug, due to factors such as the way naloxone is delivered in combination with a device and its associated DFL. Specific data are usually submitted in an application proposing approval of a nonprescription product, which may include, among other things, a LCS, HF study, and/or actual use study.

While we have defined the scope of this notice as applying to naloxone hydrochloride, nasal spray up to 4 mg and naloxone hydrochloride, autoinjector for IM or SC use up to 2 mg, FDA believes it is also important to consider other naloxone products for nonprescription use and welcomes comments from the public that could provide additional information related to the nonprescription use of these products.

While naloxone has been in use since 1971, two “community-use” naloxone products, EVZIO, a 2 mg prefilled auto-injector and NARCAN nasal spray, a 4 mg intranasal spray, have been in use for approximately 6 years, and may provide the best models to inform the public health decisions for layperson use. As discussed above, these products were designed to

facilitate use by laypersons, without medical training or the need for additional supplies or assembly before use.

Although two higher dose naloxone products, ZIMHI, a 5 mg single-dose, prefilled syringe with an integrated needle for IM or SC use, and KLOXXADO, an 8 mg nasal spray, are also considered "community use" products and have begun marketing more recently (March 2022 and August 2021, respectively), we have limited postmarketing experience to meaningfully inform whether they may be appropriate for nonprescription use. When considering risk, it is biologically plausible that there may be an association between increasing naloxone doses and the severity of precipitated withdrawal. An observational study reported that the initial dose of naloxone patients received for opioid overdose has a positive association with their likelihood to experience opioid withdrawal symptoms (Ref. 55). Causality cannot be established based on the study, however, due to concerns that differences in the opioid-dependence status and severity of opioid overdose between patients receiving a low or high initial naloxone dose were not well adjusted for in the analyses.[18] The available literature does not inform on a threshold naloxone dose above which the risk for severe adverse events would outweigh treatment benefit. Better understanding this dose-response relationship could help inform decisions about specific naloxone formulations and dosages, like higher dose naloxone, to make available for treatment in the nonprescription setting, where naloxone is unlikely to be administered by trained medical personnel. Further, ZIMHI's FDA-approved labeling includes a warning of the risk of accidental needlestick injury after use, because the needle is exposed until the safety guard is deployed (Ref. 24). For these reasons, we do not believe we have sufficient data to support a preliminary

[18] The comparison of opioid withdrawal risk between patients who received "low" (≤ 0.15 mg) and "high" (≥ 0.15 mg) initial naloxone dose did not account for whether the patient was opioid-dependent. While the study matched the two groups by respiratory rate before naloxone use and adjusted for Glasgow coma scale (as a categorical variable), overdose severity might still not be well-balanced between the two groups, given that patients in the low-dose group were less likely to have a low Glasgow coma scale (≤8) and they were more likely to receive their initial naloxone dose in the emergency department, instead of having to be treated before arriving to the emergency department.

assessment that these higher dose naloxone products could be safely used in a nonprescription setting.

With respect to naloxone supplied in other presentations including vials, ampules, or syringes without integrated needles, at this time we do not have enough data or information to support a preliminary assessment that these naloxone products have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner. The Agency is aware that community-based naloxone distribution programs have distributed these presentations of naloxone to laypeople. The availability of naloxone supplied in presentations to include vials, ampules, or syringes without integrated needles[19] for use outside of a healthcare setting through this distribution method cannot be interpreted to mean that these products are safe and effective as a nonprescription product. As discussed above, when community-based naloxone distribution programs provide naloxone to the public, it is often provided in an improvised naloxone kit whose contents can vary from one program to another. These kits may contain additional materials and instructions, such as educational materials on naloxone use, which may be a contributing factor to the safe and effective use of these products. We have no data to support that naloxone supplied in vials, ampules, or syringes without integrated needles and not accompanied by such additional materials could be safely and effectively used as directed in nonprescription drug labeling without the supervision of a healthcare practitioner.

FDA's preliminary assessment that naloxone products may be approvable as safe and effective for nonprescription use is limited to the following naloxone products:

- Naloxone hydrochloride, nasal spray up to 4 mg; and
- Naloxone hydrochloride, autoinjector for IM or SC use up to 2 mg.

[19] It is our preliminary view that these presentations generally constitute a clinically meaningful difference from the naloxone hydrochloride, autoinjector for IM or SC use up to 2 mg.

To help facilitate increased access to and availability of safe and effective naloxone products, FDA believes it is important to consider the safety and effectiveness of all naloxone products for potential nonprescription use. Therefore, we welcome comments from the public (see Section III, Request for Additional Information and Comments) with information that may inform the safe and effective use of naloxone for nonprescription use for the following products:

- Naloxone hydrochloride, injection for IV, IM, or SC use, including products greater than 2 mg; and
- Naloxone hydrochloride, nasal spray greater than 4 mg.

E. Simultaneous Marketing of Prescription and Nonprescription Naloxone

As explained above, FDA has interpreted the language in section 503(b)(4) of the FD&C Act to allow simultaneous marketing of drug products with the same active ingredient as prescription in one case and nonprescription in another only if some clinically meaningful difference, such as a difference in indication, strength, route of administration, dosage form, or patient population, exists between the drug products that makes the prescription product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer the drug. Absent a clinically meaningful difference between the products, simultaneous marketing of two drug products with the same active ingredient as, respectively, a prescription and a nonprescription drug product would result in one of the two products being misbranded.

At this time, we do not believe that any clinically meaningful differences could exist between currently approved prescription and potential nonprescription naloxone nasal spray products (up to 4 mg), or between currently approved prescription and potential nonprescription naloxone autoinjector products (up to 2 mg). For example, we do not believe that a difference in the dosage strengths within naloxone nasal spray products (i.e., 2 mg, 4 mg) by itself would be sufficient to distinguish prescription and nonprescription versions of a naloxone product without further support demonstrating that one (or more) dosage strength(s) should remain prescription because intervention of a healthcare professional is necessary for safe and effective use of the

product. Additionally, naloxone nasal spray products with the dosage strengths 2 mg and 4 mg have the same indication and minor, nonmeaningful label differences. We also do not foresee a clinically meaningful distinction between currently approved prescription and potential nonprescription naloxone products based on indication because we do not anticipate that the indication for a nonprescription naloxone product would differ from a prescription naloxone product. Additionally, the Agency does not believe there is a clinically meaningful distinction between currently approved prescription and potential nonprescription naloxone products based on differences in population because in the development of the model DFL, FDA tested the labeling across a wide range of potential nonprescription naloxone users, including adults who have and have not used opioids as well as adolescents.

It is possible that there is a potential clinically meaningful difference based on dosage strength with respect to naloxone nasal spray products (up to 4 mg) or naloxone autoinjector product (up to 2 mg) and higher dose versions of those products that would allow for simultaneous marketing of nonprescription naloxone nasal spray and prescription higher dose naloxone nasal spray, or simultaneous marketing of nonprescription autoinjector naloxone and prescription higher dose autoinjector naloxone. As discussed above, we lack data on the safety of higher dose naloxone products for nonprescription use, and we also noted that there may be an association between higher doses of naloxone and precipitated withdrawal; although at this time, we have found no causal association.

II. Notice to Current Application Holders

In this document, we provide notice of the Agency's preliminarily assessment that prescription requirements for certain naloxone products described above may no longer be necessary for the protection of the public health and that they may be safe and effective for use as directed in nonprescription labeling. As noted above, the Agency needs additional data, including product-specific data on nonprescription user interface design, including packaging and labeling, to make a conclusive determination in this respect. Additionally, we have

tentatively determined that it is unlikely that any clinically meaningful differences exist between a prescription and a potential nonprescription naloxone nasal spray product (up to 4 mg) or between a prescription and a potential nonprescription autoinjector naloxone product (up to 2 mg). Section 503(b) of the FD&C Act does not permit the simultaneous marketing of drug products with the same active ingredient as prescription and nonprescription unless there is a clinically meaningful difference between the products. If FDA makes a determination that naloxone products described in this notice are safe and effective for use without a prescription, such products would be misbranded if they bear labeling with the "Rx only" symbol. At that time, an efficacy supplement that includes product-specific data to support the nonprescription user interface design, including packaging and labeling, will need to be submitted to an approved application for a prescription naloxone product if an application holder plans to switch its naloxone product covered under the application to nonprescription marketing status in its entirety without a change in the previously approved dosage form or route of administration. The Agency strongly encourages application holders of prescription naloxone products described in this notice to contact FDA as early as possible to initiate a discussion about a possible switch.

III. Request for Additional Information and Comments

In considering additional approaches to facilitate access to naloxone, FDA is soliciting comments and information from the public in the following areas:

(1) Data to support the safe and effective use of nonprescription naloxone hydrochloride injection for IV, IM, or SC use.

(2) Data to support the safe and effective use of higher dose nonprescription naloxone hydrochloride products, such as naloxone hydrochloride, nasal spray greater than 4 mg.

(3) Any potential consequences of a switch from prescription to nonprescription status for naloxone products, and actions that FDA could consider to address them, including but not limited to, impacts on community-based naloxone distribution programs and consumers, drug shortages, and the distribution and supply of naloxone.

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the web addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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