HBW INSIGHT
CITELINE COMMERCIAL

15 Nov 2022 | **News**

US FDA Serves Notice: Approval Of OTC Naloxone Could Close Prescription Sales

by Malcolm Spicer

Agency signals assurance about making naloxone available OTC, so much so that firms with approved NDAs for Rx products should prepare for an all-nonprescription market. After offering model DFI to spur OTC switch NDAs, FDA notice about OTC assessment is second unprecedented step on its naloxone journey since opioid crisis declared a public health emergency in 2017.

The US Food and Drug Administration took a second unprecedented step in spurring development of OTC naloxone products by publishing a notice identifying data and other information needed in new drug applications for nonprescription access.

In a *notice* published on 15 November requesting comments, the agency signals that it is becoming assured about making naloxone available OTC, so much so that firms with approved NDAs for Rx products using a variety of delivery formats should prepare for an all-nonprescription market.

The Center for Drug Evaluation and Research states, "we provide notice" to current naloxone NDA holders about the FDA's "preliminarily assessment that prescription requirements for certain naloxone products … 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."

Firms with approved NDAs for Rx naloxone are *Emergent BioSolutions, Inc.*, Kaleo Inc. and *Hikma Pharmaceuticals plc*.

The preliminary assessment, which supported OTC access up to 4-mg nasal spray and up to 2-mg autoinjector for intramuscular or subcutaneous delivery, targets facilitating development and approval of nonprescription naloxone products.

HBW INSIGHT
CITELINE COMMERCIAL

The CDER adds, though, that the notice "is not a final determination that certain naloxone drug products are safe and effective for nonprescription use, and it does not mandate an" immediate OTC switch for a naloxone product.

FDA regulations don't permit simultaneous prescription and nonprescription marketing of the same drug with the same active ingredient without "a clinically meaningful difference between them," the center explains. That means "if and when FDA has sufficient data to support approval of a nonprescription naloxone product ... currently marketed naloxone products labeled as 'Rx only' with no clinically meaningful difference from the approved nonprescription products will be considered misbranded."

Naloxone Switch NDA Submitted As US FDA Signals Nonprescription Access Looks Safe, Effective

By Malcolm Spicer

15 Nov 2022 Harm Reduction Therapeutics submits NDA for OTC approval of a 3-mg naloxone nasal spray branded RiVive. CEO Michael Hufford says the NDA touches all the bases FDA detailed in notice it published on what's needed in naloxone OTC switch proposals. *Read the full article here*

Califf Tipped FDA's Hand

The "Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use" notice comes after FDA Commissioner Robert Califf said the agency was working on providing motivation for more companies to propose OTC access to the nonselective opioid receptor antagonist

In April, Califf signaled the direction the agency was heading in its OTC naloxone push, saying it was looking "to exert some changes compared to the usual way of doing business to make this happen." The usual way, developing switch NDAs for OTC drugs with outlooks for huge revenues, wasn't working for naloxone, he said at a conference. (Also see "*OTC Naloxone May Get Another Push From US FDA As Agency Prepares Novel Switch Proposed Rule*" - HBW Insight, 3 May, 2022.)

The notice released a day ahead of publication in the Federal Register also comes as Califf has assured Capitol Hill that the agency would deliver results from its study on responding to the opioid abuse crisis, leading to an overdose prevention framework published in August. (Also see "*US FDA Expects No Change In Naloxone Access Barrier If Prices*

Compare Bioavailability, Systemic Absorption To Approved Product

In addition to human factors studies, the

High For Potential OTC Products" - HBW Insight, 30 Aug, 2022.)

The center's decision on an OTC switch could be a year away. That's because Harm Reduction Therapeutics Inc., a nonprofit firm launched to make naloxone available OTC at little or no cost to consumers, in late October submitted to the FDA the first NDA for a naloxone switch, a 3-mg nasal spray branded RiVive *(see related story)*.

First Model DFL, Now NDA Details

HRT's launch in 2017 followed the FDA's first unprecedented step in its OTC naloxone work. The agency for the first time provided a model Drug Facts label, from a study it commissioned, for potential sponsors to use in preparing naloxone OTC switch NDAs. (Also see "*FDA Has Model Drug Facts Labels For OTC Naloxone, Wants Switch Proposals*" - HBW Insight, 17 Jan, 2019.)

The FDA's notice about its OTC assessment is the second unprecedented step on its naloxone journey since the opioid crisis, which encompasses misuse, abuse and overdose deaths involving illicit and prescription opioids, was declared a public health emergency in 2017.

"FDA has taken quite a few, I think, unprecedented actions to try to speed along a development program for an OTC version of these drugs," said food and drug regulation attorney Deborah Livornese.

CDER states applicants proposing novel naloxone products, including nonprescription, should demonstrate sufficient systemic absorption of the ingredient as well as rapidity of onset compared to an approved product, particularly in the early critical period after drug administration.

However, the FDA determined it isn't necessary for applicants to conduct clinical efficacy trials as effective doses have already been established. Instead, efficacy can be based on information known about other naloxone products and supported by a relative bioavailability study conducted in healthy volunteers.

NDA also sponsors may need to provide additional data, such as literature reviews, to support the safety and effectiveness of their products if exposure is different.

In addition to stating requirements for a naloxone OTC switch to facilitate additional approaches, the FDA requests data to support safe and effective use of nonprescription naloxone intravenous, intramuscular or subcutaneous injection and use of higher dose nonprescription naloxone, such as a nasal spray greater than 4 mg.

The CDER also asks for comments on potential consequences of an Rx-to-OTC switch for naloxone products and actions the FDA could consider in response, including impacts on community-based naloxone distribution programs and consumers, drug

In the notice, the FDA continues the detail and specificity for an OTC naloxone NDA it offered with the model DFL.

"I think the bottom line is for FDA, for these kinds of products, is that they can't do anything unless somebody shows up with an application, a reasonably good application," said Livornese, a director at Hyman, Phelps & McNamara PC in Washington.

shortages and the distribution and supply of naloxone.

Naloxone currently also is available in IV injectors, but the delivery format isn't compatible with nonprescription use.

"It's a kind of roadmap to what needs to be done, to get approval. I mean they've been really specific. Because we have the Drug Facts label, you don't have to do label comprehension studies, except for the extent you want to change the label," she added.

Consumer Healthcare Products Association executive Barbara Kochanowski described the notice as "a novel way to have a conversation" about information needed for OTC naloxone approval. "My first reaction was, 'Wow, ever saw something like this before?'" said CHPA's senior vice president, regulatory and scientific affairs.

"In terms of serving public health, it's great that FDA has assembled all of this history about naloxone, and carefully laid out how we got to where we are today, and how we might go forward to see OTC naloxone," Kochanowski added.

Although making naloxone available OTC hasn't been the most high-profile topic among FDA news, the Federal Register notice should expand its profile.

"Certainly, Federal Register notices get out there, they get to people, they can have comments and people reacting. It feels like an invitation for people to send information, especially data with FDA being a data-driven organization," Kochanowski said.

The CHPA will work with its members on submitting comments to the FDA on the notice.

The FDA stated in the notice that its review of market data showed a substantial increase in naloxone nasal spray distribution drove 81% growth in national sales and dispensed prescriptions for naloxone products across all healthcare settings from around 5.1m units in 2017 to around 9.3m units in 2021.

Injectable and nasal spray sales to hospitals increased by more than 50% during the period and sales to retail pharmacies tripled. In 2017, around half naloxone sales to retail pharmacies were

for nasal sprays and by 2021 more than 90% were for the nasal spray.

The notice also states data show more than 80,000 people in the US died of opioid-involved overdoses in the 12-month period through January 2022, 75% of all drug overdose deaths. Opioid-involved overdose deaths increased from 71,000 in 2021.

In addition to pushing for change on the naloxone front, Califf gave opioids and other controlled substance programs a higher profile at the agency in July by appointing Marta Sokolowska CDER deputy director for substance use and behavioral health. (Also see "*US FDA Elevates Controlled Substances Coordinator To New Deputy CDER Director Role*" - Pink Sheet, 18 Jul, 2022.)