FENTANYL ADULTERATED OR ASSOCIATED WITH XYLAZINE IMPLEMENTATION REPORT

JUNE 2024

THE WHITE HOUSE
EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF NATIONAL DRUG CONTROL POLICY

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Preface from Dr. Gupta, Director

The United States faces an evolving challenge from the increasing presence of xylazine in the illicit drug supply, primarily but not exclusively found in combination with fentanyl. For this reason, on April 12, 2023, I designated fentanyl adulterated or associated with xylazine (FAAX) as an emerging drug threat, based on authorities provided to me as Director of National Drug Control Policy. The Biden-Harris Administration convened a federal interagency Fentanyl Adulterated or associated with Xylazine Interagency Working Group (FAAX-IWG), and has already taken significant action to better protect Americans from this threat. The Office of National Drug Control Policy (ONDCP) coordinated and released a comprehensive government-wide response plan to this threat in the summer of 2023, outlining high priority actions needed. These promising efforts, which will have immediate as well as long-term impact in protecting the health and safety of Americans, are described in this implementation report.

Xylazine is a veterinary tranquilizer that is not approved for use in humans. This drug is not regulated under the Federal Controlled Substances Act, and historically has been thought to be associated with a low risk of illicit use. However, when consumed in combination with fentanyl, individuals can suffer severe consequences including extreme sedation and deep skin and soft tissue injuries. Further, people chronically exposed to FAAX often struggle with difficult withdrawal symptoms that may present unique treatment challenges compared to opioid withdrawal alone. While some people who use opioids seek out xylazine and others seek to avoid it, research suggests that people who use opioids in combination with stimulants are more likely to encounter FAAX, compared to people who use only opioids. Thus, in addition to being treated for harms from xylazine, people exposed to xylazine may need treatments for other use disorders. Fortunately, there are emerging protocols to prevent xylazine-involved overdoses, ease withdrawal symptoms, and manage an effective treatment and recovery process for people with opioid use disorder (OUD) who are chronically exposed to FAAX.

The reality of this evolving synthetic drug threat has become clearer following the initial emerging threat designation, as more state and local health authorities, hospitals, and treatment centers have begun testing for xylazine. This is truly now a national threat. I strongly encourage both public health and public safety agencies to intensify their efforts to monitor this threat and to ensure that every individual impacted by xylazine receives the assistance they require. As outlined in the implementation report that follows, federal agencies are taking numerous steps to support such urgently needed efforts to save lives.

Rahul Gupta, MD, MPH, MBA
Director of National Drug Control Policy

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Part I: Introduction

On April 12, 2023, Dr. Rahul Gupta, Director of National Drug Control Policy, formally designated fentanyl adulterated or associated with xylazine as an emerging drug threat, pursuant to 21 U.S.C. § 1708. According to authorities provided to ONDCP by Congress in 2018, such a designation triggers a number of follow-on requirements, including the publication of a Response Plan.

In close consultation with other National Drug Control Program Agencies (NDCPAs), ONDCP developed the *Fentanyl Adulterated or Associated with Xylazine Response Plan* (FAAX Plan), which was published in July of 2023.[1] This *Implementation Report* on the FAAX Plan is also required by the Congress each year until such time as ONDCP formally de-designates the threat.

The remainder of the implementation report consists of a brief summary of the xylazine/fentanyl threat based on the best available information (part II); an update of progress made by the Biden-Harris Administration in implementing the FAAX Plan (part III); and a brief conclusion (part IV).

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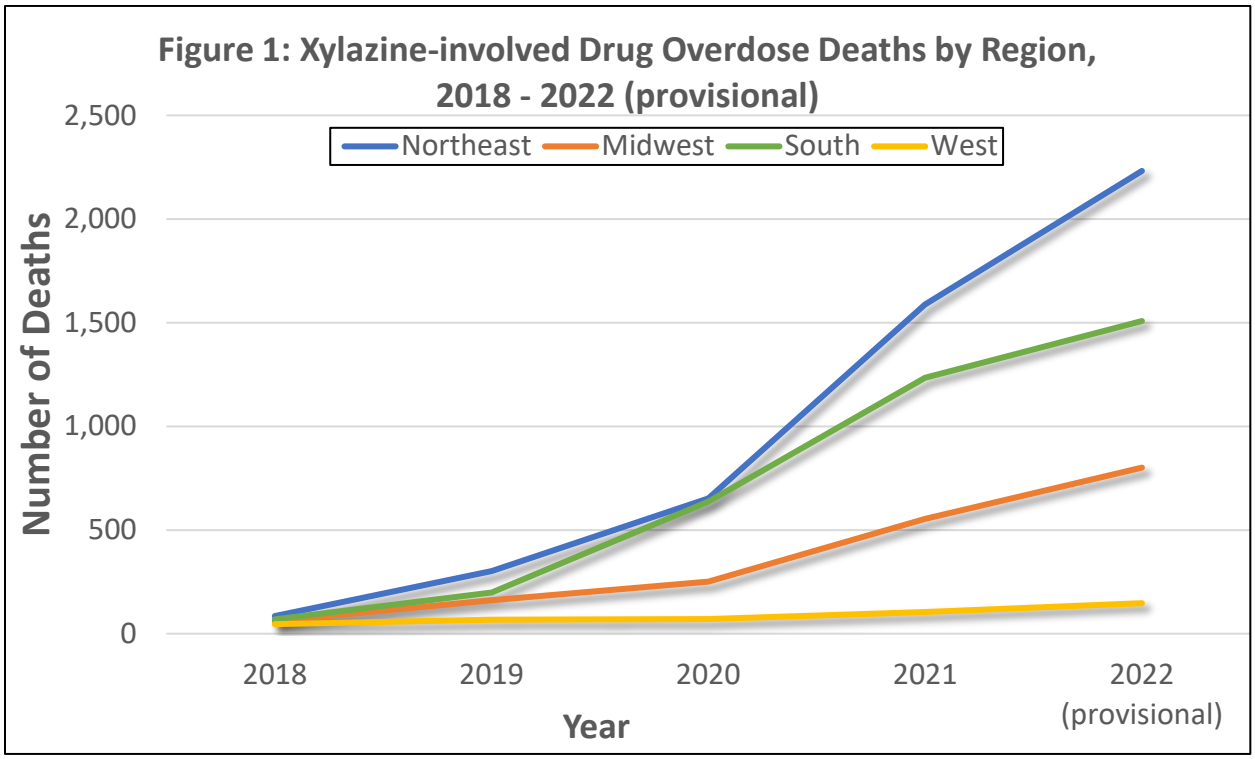
Part II: The Challenge Posed by FAAX

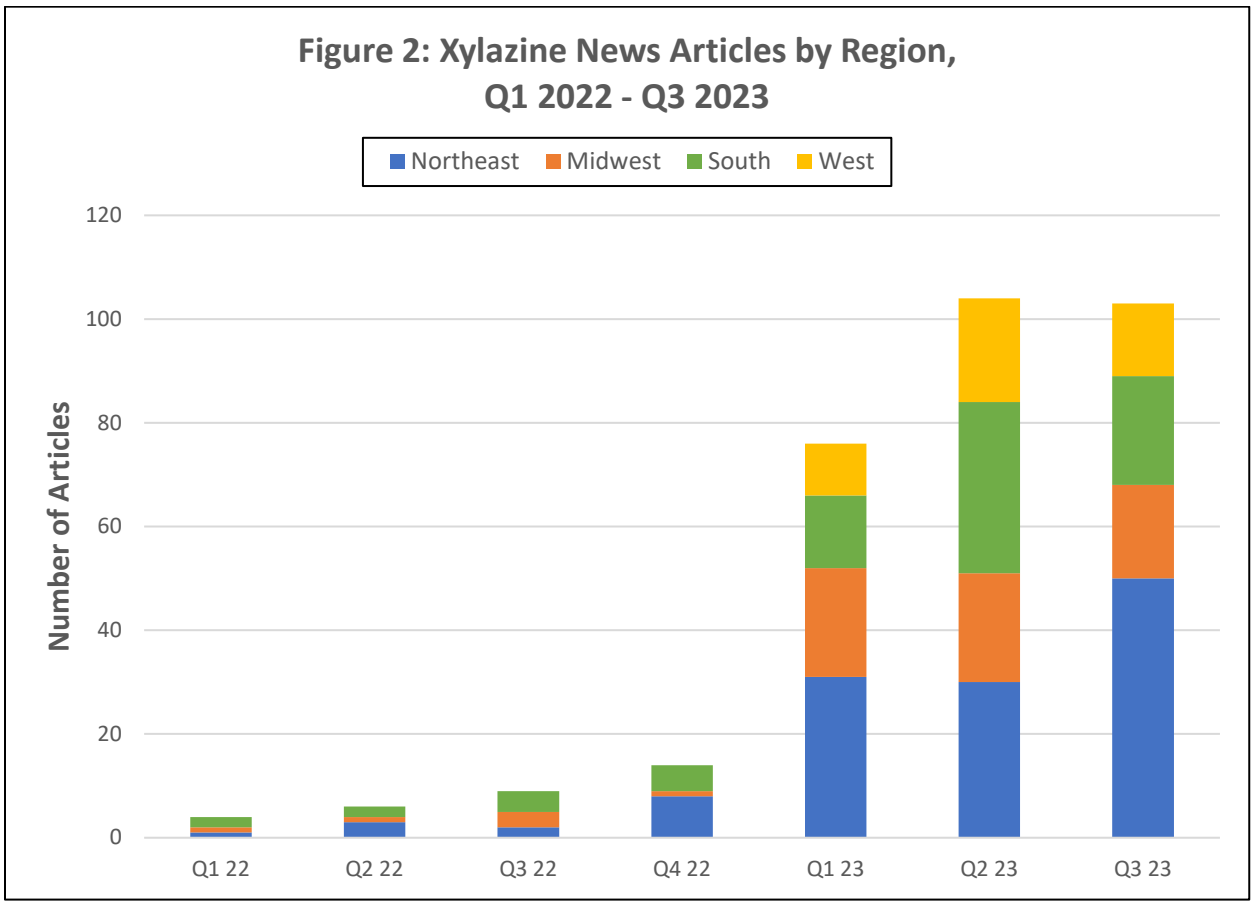
In April 2023, the ONDCP Director formally designated fentanyl when combined with or occurring with xylazine as an emerging drug threat. Following the designation, the Administration began immediately drafting a federal government response plan. Xylazine – a veterinary tranquilizer that has not been approved by the Food and Drug Administration (FDA) for human use – is a central nervous system depressant that can cause drowsiness and amnesia and slow breathing as well as reduce blood pressure and heart rate.[2] Unlike opioids, there is no antidote to rapidly reverse a xylazine overdose.

The FAAX Plan, disseminated in July 2023, requires federal agencies to enhance xylazine testing, treatment, and supportive care protocols; develop comprehensive data collection systems; refine ongoing strategies to reduce the illicit supply of xylazine; and support the rapid conduct of research on several important questions about xylazine, especially to deepen our understanding of how xylazine and fentanyl interact. Significant progress, outlined in the next section of this report, has already been made. First, expanded xylazine testing and studies on the prevalence of xylazine across the United States are providing a clearer picture of xylazine's penetration in the illicit drug supply. Until recently, medical tests for substance use after an overdose or as part of a treatment intake did not include testing for xylazine. However, as more regular testing for the substance is taking place and more data is coming in, the increasing national, regional, and local threat posed by xylazine use and its outcomes is becoming apparent.



As Figure 1 illustrates, identification of xylazine-involved overdoses have been sharply increasing over the last several years. Xylazine alone has risks, but the combination with other drugs such as fentanyl pose serious health risks to Americans. The combination with other

substances – especially, but not only fentanyl – has been detected in a growing number of overdoses.[3] During 2021, almost 3,500 xylazine-involved deaths were reported, more than double the previous year.



In addition to monitoring the spread of xylazine-involved overdose deaths by region, tracking state and local xylazine news articles offers insight into how this emerging drug threat is spreading and how communities are responding. A sample of open-source state and local news articles published between January 2022 and September 2023 was gathered, and as shown in Figure 2, the number of xylazine-related articles increased substantially over the study period. Similar to the geographic spread of xylazine-related deaths, the news reports were predominantly published in the Northeast, South, and Midwest. The content of these state and local news articles highlights important issues ranging from reports of xylazine arrival in the local drug supply to the harm reduction responses that community groups are taking to combat xylazine's effects.

The consequences of xylazine consumption began to gain significant attention in the Kensington section of Philadelphia in 2019, when consumers of FAAX presented to hospitals both because of overdoses and due to serious skin injuries associated with xylazine. Healthcare providers were initially unaware that the symptoms and injuries they were observing were associated with xylazine. Clinicians faced challenges treating wounds and retaining patients in care due to severe withdrawal symptoms associated with discontinuing FAAX.

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Local, state, and federal efforts to widely distribute opioid overdose reversal medications like naloxone have saved lives from overdose and, with linkage to follow-up care, have even helped people seek out effective addiction treatment. Although it is now known that it is critical to give naloxone to a FAAX-exposed person, when FAAX initially appeared, first responders and those offering harm reduction services faced overdose victims who seemed unresponsive to naloxone due extreme sedation caused by xylazine. Over time, first responders discovered that when fentanyl is combined with xylazine, naloxone remains a critical part of overdose response, and that, individuals may require complementary measures such as mechanical airway support, supplemental oxygen, and support for longer periods of time to obtain responsiveness following an overdose.

When individuals abruptly stop regularly using fentanyl combined with xylazine, they often experience severe withdrawal symptoms. Attempts to treat those symptoms are often stymied because the withdrawal symptoms caused by xylazine go unrecognized. Rapid testing for the presence of xylazine in a patient presenting to the Emergency Department (ED) or hospital often is not available, which makes it more difficult for the provider to recognize that the observed symptoms are due to xylazine withdrawal. Without that recognition, medical personnel use medications for OUD, which although important, are insufficient to effectively treat xylazine withdrawal. New treatment protocols are being developed and deployed to ensure that patients experiencing xylazine withdrawal symptoms can be properly treated.

Xylazine-associated wounds can cause serious injury, potentially leading to amputations if they are not adequately treated. Importantly, several doctors who practice in areas of the country where xylazine use is more common have developed ways to treat these wounds and improve patient outcomes, including cleaning the wounds with saline solution and dressing them with petroleum infused gauze.[4]

This is a good start, but there is much more to do. Every week there are reports of xylazine spreading to new counties across the country. This national threat requires the ongoing attention of public safety and public health officials everywhere.

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Part III: FAAX Plan Actions Progress Update

This section provides an update on progress in implementing action items from the FAAX Plan. As in the original FAAX Plan, the action items are broken down by the six pillars:

1. Testing
2. Epidemiology and Comprehensive Data Systems
3. Evidence-Based Prevention, Harm Reduction, and Treatment Implementation and Capacity Building
4. Source and Supply Information and Intelligence, and Supply Reduction Actions
5. Regulatory Control and Monitoring Options
6. Basic and Applied Research

TESTING

Law Enforcement Testing for Xylazine (Drug Enforcement Administration (DEA))

DEA currently tests for xylazine in all samples it receives for analysis and evaluation. It maintains information regarding the prevalence of xylazine in those samples, which it will continue to use to provide information and reports regarding the dangers of xylazine to the public.

Testing of Border Drug Seizures (Customs and Border Protection (CBP))

CBP's Laboratories and Scientific Services (LSS) tests drugs seized at the border, in air cargo, private mail delivery services' facilities, and in other settings where inspections occur. LSS currently monitors trends for several drugs, including fentanyl, fentanyl with xylazine, and xylazine. This testing helps identify the circumstances under which drug traffickers are introducing xylazine into drug products, which provides important information about how the threat is evolving. LSS will continue testing interdicted samples for the presence of xylazine and report its presumptive monthly findings from initial tests to law enforcement partners help identify and track trends over time.

Diagnostic Tests (FDA)

FDA is collaborating with federal government partners and other stakeholders, including industry, to help facilitate development of *in vitro* diagnostic tests, such as those intended to detect xylazine in human specimens at point-of-care (for example, visually read test strips that would rapidly detect xylazine in human urine). FDA will continue to encourage test developers to work with FDA to develop and get these tests to market.

Overdose Data to Action (Centers for Disease Control and Prevention (CDC))

The Overdose Data to Action (OD2A) in states notice of funding opportunity[5] funds health departments in 49 states and Washington, D.C. to improve surveillance and prevention of drug overdose, including xylazine-involved overdose. In addition, jurisdictions can use funding to conduct comprehensive toxicological testing of drug overdose deaths suspected to involve opioids and/or stimulants. OD2A: Limiting Overdose through Collaborative Actions in Localities currently funds 40 city, county, and territorial health departments to improve surveillance and prevention of drug overdose. This funding includes supporting medical

examiner and coroner offices to improve the comprehensiveness and/or timeliness of toxicologic testing of suspected drug overdose deaths, for xylazine and other substances. OD2A: Limiting Overdose through Collaborative Actions in Localities (OD2A: LOCAL) funds enable states and localities to purchase xylazine test strips (XTS) for the purposes of drug checking, consistent with the governing statutory authority and federal, state, and local law.

State Opioid Response (Substance Abuse and Mental Health Services Administration (SAMHSA))

SAMHSA, along with other Operating Divisions of the Department of Health and Human Services (HHS), has recently highlighted the broad allowance of several of its grant programs to support the purchase of XTS for drug-checking purposes if requested , and it is permissible under federal, state, and local law. These include the State Opioid Response (SOR) grants, and the Substance Use Prevention, Treatment, and Recovery Services (SUPTRS) Block Grant. Other grants that allow for XTS purchases include Prevent Prescription Drug/Opioid Overdose-Related Deaths grants, and First Responders-Comprehensive Addiction and Recovery Act (FR-CARA) grants.

Rural Communities Opioid Response Program (Health Resources and Services Administration (HRSA))

Grant recipients of the Rural Communities Opioid Response Program may use their HRSA-resources to purchase drug-checking xylazine testing supplies (where permissible under federal, state, and local laws) within their community settings to enhance the effectiveness of harm reduction activities.

Xylazine Testing for Veterans (Department of Veterans Affairs (VA))

Xylazine testing is already offered by VA through accredited commercial reference laboratories for testing in blood, serum, or urine using mass spectrometry-based laboratory developed tests. After FDA-cleared clinical tests for xylazine become available, VA will convene a collaborative workgroup to develop guidance for internal implementation and use. Additional guidance will also be developed in the event of availability of FDA cleared point of care testing for xylazine.

Testing within Federal Prisons (Bureau of Prisons (BOP))

BOP is developing methods to improve communication between custody and health services staff members when illicit substances are identified within a facility. Such communication will allow BOP to respond with improved surveillance, testing, and focused education to employees and adults in custody.

EPIDEMIOLOGY AND COMPREHENSIVE DATA SYSTEMS

Testing Xylazine Seizures (DEA, FDA and CBP)

DEA continues to test for xylazine in all samples it receives, and has seen a steady increase in the percentage of fentanyl seizures that contain xylazine. In 2024, 36 percent of fentanyl powder samples and nearly 6 percent of fentanyl pills are adulterated with xylazine. In addition, DEA has worked to develop the Joint INTREPID Lab, in collaboration with CBP and FDA, to work collaboratively to provide actionable intelligence, scientific support, and research to law enforcement. As part of the lab's first intelligence product, DEA and its partners developed testing to determine the source of specific xylazine samples. These efforts now allow DEA to

determine whether specific samples of xylazine have been either diverted from the veterinary supply chain in liquid form or procured in solid or powder form from the People's Republic of China (PRC) or other countries.

Assessing Xylazine Monitoring Methods (National Institutes of Health (NIH))

NIH's National Institute on Drug Abuse's (NIDA) National Drug Early Warning System (NDEWS) is evaluating novel methods to sample, test, and monitor xylazine use, including Emergency Medical Services (EMS) call data as well as sampling and testing wastewater. NDEWS has 16 sentinel sites across the United States that use a variety of drug monitoring technologies covering several states (Florida, Kentucky, Michigan, Minnesota and Texas) and many large metropolitan areas including Atlanta, Chicago, Denver, Detroit, Los Angeles, New York City, Phoenix, San Diego, San Francisco, Seattle, St. Louis, and Washington, D.C. NIDA provided Fiscal Year (FY) 2023 supplemental funding to NDEWS to expand wastewater sampling for xylazine and other drugs within its network. NIDA also funded a project to Biobot Analytics to examine performance of its wastewater sampling technology to monitor community-level use of illicitly traded drugs, including xylazine, on a national scale.

Emergency Department Reporting (SAMHSA)

SAMHSA's Drug Abuse Warning Network (DAWN) program is a nationwide public health surveillance system that provides timely data on emerging trends in substance use. It works by capturing data on ED visits related to recent substance use and misuse directly from the electronic health records of participating hospitals. As EDs continue to add xylazine testing, DAWN will provide a more accurate national picture of xylazine-related incidents.

State Unintentional Drug Overdose Reporting System (SUDORS) (CDC)

CDC's OD2A program supports jurisdictions in collecting high quality, comprehensive, and timely data on nonfatal and fatal overdoses inform prevention and response activities. SUDORS uses data from death certificates, medical examiner and coroner reports, and full medical toxicology reports to describe trends in drug overdose deaths, identify key circumstances surrounding overdose deaths, and identify emerging substances involved in those deaths, such as xylazine to help inform overdose prevention and response efforts.

The SUDORS dashboard provides comprehensive information on drug overdose deaths.[6] Rates and percentages of overdose deaths where select drugs of interest were detected, including xylazine, are displayed numerically and through a state-by-state map. SUDORS data show overdose deaths where xylazine was detected have been steadily rising. Among participating jurisdictions that met public reporting requirements (reporting all overdose deaths in their jurisdiction for the selected year and had medical examiner or coroner reports for at least 75 percent of deaths in that year), xylazine was detected in 3.7 percent of overdose decedents in 2020; in 2022, that number rose to 6.6 percent.

CDC has published a Morbidity and Mortality Weekly Report focused on xylazine using the summarized data from the SUDORS dashboard. Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022 used findings from the CDC's analysis of the monthly percentage of illegally manufactured fentanyl (IMF)-involved deaths with xylazine detected. Findings include a 276 percent increase in deaths among 21 jurisdictions from January 2019 (2.9 percent) to June 2022 (10.9 percent).

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Investigating Overdose Deaths in Federal Prisons (BOP)

BOP established an Overdose Death Review Panel, reviewing 30 different variables and evaluating for patterns and trends that may help inform its efforts to reduce drug overdose. A centralized electronic repository has been developed to allow for historical trending and analysis by BOP Population and Correctional Health Branch epidemiologic employees. BOP will explore opportunities to increase the testing for xylazine and monitor results as part of the overdose death review.

EVIDENCE-BASED PREVENTION, HARM REDUCTION, AND TREATMENT IMPLEMENTATION AND CAPACITY BUILDING

Harm Reduction Strategies (NIH)

NIDA's new harm reduction research network,[7] funded by NIDA as part of the NIH Helping to End Addiction Long Term (HEAL) Initiative®, is poised to develop and evaluate harm reduction strategies for xylazine exposure. Lead HEAL network sites are located in Baltimore, Chicago, New York City, and other locations where xylazine has become highly prevalent. Current NIDA-funded research is engaging people who use opioids to understand their experiences with xylazine exposure to inform harm reduction strategies.

Homelessness and Xylazine (HRSA)

HRSA has a cooperative agreement with the National Health Care for the Homeless Council to develop, deliver, and coordinate training and technical assistance for health centers to respond to the needs of people experiencing homelessness or who are unstably housed. In March 2023, the National Health Care for the Homeless Council developed a health care provider guide, *Substance Use Guidelines: Xylazine*, that informs providers serving individuals experiencing homelessness of treatment models of care, considerations, and treatment and support services to address xylazine use risks and treatment following an exposure.

First Responders-Comprehensive Addiction and Recovery Act Grants (SAMHSA)

SAMHSA's FR-CARA grants allow for the purchase of XTS for drug checking purposes. Funds must be used for training and providing resources for first responders and members of other key community sectors to protect themselves from exposure to dangerous substances and to respond appropriately when exposure occurs. Grantees train first responders on carrying and administering medications for emergency reversal of known or suspected opioid overdose and provide resources. Recipients also establish processes, protocols, mechanisms for referral to appropriate treatment and recovery support services, and safety around fentanyl and other substances, including xylazine.

Stop Overdose Campaigns (CDC)

CDC will continue to implement the Stop Overdose Campaigns, which aim to educate younger audiences about preventing overdose and substance use-related harms. The Campaigns focus on raising awareness of increased risk associated with fentanyl and polysubstance use, overdose treatment (e.g., naloxone), and reducing stigma around recovery and treatment options. CDC created dedicated social media posts and graphics around xylazine and will integrate xylazine messaging into existing Stop Overdose web content as well into other events and activities related to overdose, including International Overdose Awareness Day.[8] CDC will further integrate xylazine messaging into future campaign efforts.

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On February 29, 2024, CDC provided a Clinical Outreach and Community Activity (COCA) Call centered around xylazine[9]. This call discussed the epidemiology of xylazine-associated overdoses, the current understanding of health risks related to exposure to fentanyl associated with xylazine, and acute overdose treatment strategies. CDC offers a comprehensive online resource titled "What you should know about Xylazine."[10] This webpage equips individuals with valuable information about Xylazine, its effects, and crucial steps to take in case of an overdose. Additionally, CDC conveniently links to a dedicated resource page[11] from state and local health departments, providing further support and guidance.

Treatment and Harm Reduction for Veterans (VA)

VA will develop and deploy a treatment framework, develop and utilize overdose treatment and other harm reduction strategies, promote capacity building among service providers, and educate the public. VA's efforts will be informed by its award-winning approach to implementing its Rapid Naloxone Initiative.[12] VA will also:

- Develop patient and provider education on xylazine with patient and provider educational brochures;
- Work with Office of Nursing Services to develop xylazine-related wound care guidance with a goal of having guidance developed in FY 2024;
- Deliver, through academic detailing, knowledge translation services to clinicians, Veterans and staff; and
- Continue to disseminate the most up-to-date emerging practices to support clinical care to patients exposed to xylazine—including response, clinical stabilization, withdrawal management, and treatment guidance.

Educating Federal Prison Staff of Xylazine Threat (BOP)

BOP developed a Clinical Alert highlighting the dangers of xylazine and distributed it to all BOP Clinical Directors and Health Services Administrators in November 2022, and again in August 2023. BOP is currently working to develop messaging for adults in custody that will be distributed to educate them on illicit drug contamination with xylazine and the associated risks. BOP is also planning to educate all Institutional Quality Improvement/Infection Prevention & Control Officers on the risks of xylazine, the importance of active surveillance to identify when xylazine may have been introduced to the prison population within an institution, and methods to rapidly develop a targeted institutional response plan.

Capacity Building in Rural Areas (Department of Agriculture (USDA)

USDA's Rural Development Distance Learning and Telemedicine (DLT) Grant Program helps rural communities acquire the technology and training necessary to connect educational and medical professionals with students, teachers, and patients in rural areas. Successful applicants have used DLT grants to support equipment, software, and facilities to conduct telehealth with patients, education with healthcare providers, specialized workforce training, and provide educational opportunities for students in remote areas to access instruction not available locally. DLT projects may support efforts to increase access to prevention interventions, treatment best practices, and harm reduction methods in educational settings, including interventions related to fentanyl adulterated with xylazine.

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Additionally, the USDA National Institute of Food and Agriculture's (NIFA) Rural Health and Safety Education (RHSE) Grant Program funds community-based outreach education programs. In 2023, the RHSE Grant Program specifically requested projects that provide information to support the utilization of telehealth, telemedicine, and distance learning plans for opioid and substance education and training in rural communities. Projects funded under this program could include training to recognize overdoses with fentanyl adulterated with xylazine and providing recommendations for the appropriate response in seeking care for overdoses from fentanyl adulterated with xylazine.

SOURCE AND SUPPLY INFORMATION AND INTELLIGENCE, AND SUPPLY REDUCTION ACTIONS

Combating Xylazine Smuggling (FDA)

In February 2023, FDA announced that it took action to restrict the unlawful entry of xylazine active pharmaceutical ingredients and finished dosage form drug products into the country to address a growing public health concern.[13] The issuance of Import Alert 68-20,[14] "Detention Without Physical Examination of Xylazine Active Pharmaceutical Ingredient (API) and Unapproved Finished Drug Products Containing Xylazine," has allowed FDA to better ensure that xylazine is being directed to legitimate uses for animals. FDA's import screening systems automatically identify incoming shipments of products and firms on an import alert, and FDA can detain them without physical examination. Such actions have resulted in four firms being added to the import alert list.

Sourcing and Seizing Xylazine Imports Intended for Illicit Use (DEA)

DEA collaborates with other agencies to identify sources of xylazine that are used for illicit purposes. Xylazine intended for illicit human use enters the United States three ways: in solid form from the PRC and other countries; as diverted solution from veterinary supply chains; and mixed with fentanyl seized at the southwest border. DEA has developed testing to determine whether specific samples of xylazine intended for human use were diverted from veterinary supply chains; DEA found that 17 percent of tested xylazine came from liquid veterinary preparations and the remaining 83 percent came from solid forms. DEA has also seized xylazine as part of criminal investigations, including seizing xylazine-fentanyl mixtures in 48 states and in the District of Columbia. As part of Operation Chem Capture, DEA agents seized xylazine in powder form shipped from a company in the PRC to Miami, and paid for in Bitcoin. That same company shipped xylazine to a fentanyl trafficker in Philadelphia multiple times a month. When agents conducted a search of the trafficker's home, they found 1,500 counterfeit pills, two pill presses, a powder mixture of fentanyl and xylazine, and two bottles of liquid xylazine (diverted from veterinary supply chains).

Gaining Insight into the Xylazine Supply Chain (CBP)

CBP continues to gain increased insight into the xylazine supply chain through its ongoing enforcement actions. For example, CBP scientists are working with DEA and FDA scientists on analytical methods to trace the source of seized xylazine and to promote additional sharing of seized samples, data, and testing results. CBP palynologists will conduct pollen analysis on interdicted xylazine samples to identify where the product was manufactured. CBP primarily has encountered xylazine in powder form within the air cargo and express consignment environments originating almost exclusively from companies based in the PRC. CBP xylazine

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detections at the southwest border (SWB) constitute a very small percentage (less than 2 percent) of overall SWB fentanyl seizures and are typically small load sizes.

Investigating Xylazine Traffickers (Homeland Security Investigations (HSI))

HSI will continue to work closely with CBP's National Targeting Center and with investigative partners like the FDA and DEA to identify and target transnational criminal organizations and their supply chains that acquire materials, like xylazine, to produce illicit synthetic drugs. When xylazine is encountered from high-risk shippers and consignees who are moving illicit synthetics into the United States via shipments, HSI responds to employ immediate investigative operations. The Office of Intelligence and Analysis will continue to produce strategic intelligence on the emergence of xylazine as an adulterant within the illicit fentanyl supply chain. This effort consists primarily of identifying sources of supply, diversionary tactics, concealment methods, and opportunities to disrupt these smuggling tactics.

Training Canine Teams (CBP)

CBP will train precursor, xylazine, and ketamine scent capability to six Office of Field Operations Canine Teams. These trained canine teams will deploy to air cargo, express consignment, and international mail facilities in key locations.

Monitoring Xylazine Imports (FDA and CBP)

FDA has partnered with CBP to share data, enhance the monitoring of imported xylazine to verify that the recipients are known or registered entities within the legitimate animal drug supply chain or research arena, and combat illicit shipments. Through this partnership and collaboration, FDA and CBP are exchanging vital supply chain information to bolster risk targeting and surveillance efforts. By leveraging certain supply chain data, FDA and CBP can better focus on intercepting and deterring future unlawful shipments while allowing the release of compliant trade.

Investigating Xylazine Diversion (FDA)

To help effectively disrupt the sources of xylazine destined for unapproved illicit human use, FDA is focusing its resources on continuing to investigate those who are involved in the possible diversion of xylazine from the legitimate supply chain; identifying and investigating the possible unlawful importation of xylazine into the United States through the ports of entry (POE); and evaluating online marketplaces to identify the possible unlawful sale of xylazine on the Internet. FDA is actively collaborating with law enforcement agencies, DEA and HSI to exchange information related to the supply of xylazine.

REGULATORY CONTROL AND MONITORING OPTIONS

Supporting Drug Scheduling Decision Making (FDA and DEA)

Per the statutory provisions of the Controlled Substances Act (CSA, at 21 U.S.C. § 811(a–c)), DEA requested that HHS conduct a scientific and medical evaluation and make a scheduling recommendation regarding xylazine. FDA would perform those functions, on behalf of HHS, and look at eight factors specified in the CSA to determine a drug's abuse potential, whether it has accepted medical use in the United States, and the extent to which it has dependence liability. Because of the eight statutory factors involved in FDA's assessment, it is often referred to as the Eight-Factor Analysis (8FA). DEA's scheduling determination is informed by HHS's evaluation

and recommendation, which is binding as to scientific and medical matters. FDA will continue to work with HHS and DEA as requested. Further, agencies will continue to provide Congress with technical assistance with respect to legislative efforts to control xylazine in Schedule III. The Administration has also submitted a legislative proposal to Congress that makes xylazine a Schedule III drug and generally addresses scheduling, reporting, and sentencing related to xylazine.

Monitoring Supply Chains (FDA)

FDA will continue to engage and collaborate with other government agencies to ensure information sharing, data driven strategies, and coordinated efforts to interdict illicit products offered for import. The joint National Operational Strategy will launch in FY 2024 to provide surveillance and monitoring of unapproved drug supply chains. Interdiction efforts to help identify and investigate the possible unlawful importation of xylazine will be focused on key land border POEs, international mail facilities, and express courier hubs across the nation.

BASIC AND APPLIED RESEARCH

Developing Effective Treatments for Xylazine Harms (FDA and NIH)

FDA has provided information about xylazine and reversal agents used in animals to federal partners to facilitate research efforts. FDA is conducting *in vitro* studies that aim to describe the human metabolism of xylazine and combinations. In addition, NIH/NIDA is funding a study of xylazine and fentanyl metabolism in individuals who present to the ED after a FAAX-involved overdose.[15] The outcome of these studies is expected to inform the design of subsequent research studies that will address matters related to the toxicology of this drug, including the induction of skin lesions.

FDA, in collaboration with the Reagan Udall Foundation, held a public meeting[16] on October 4, 2023 to explore strategies for drug development and clinical research that supports the mitigation and reduction of risks associated with human exposure to xylazine. FDA provided funding to and is collaborating with Research Triangle Centers of Excellence in Regulatory Science and Innovation to facilitate the scientific investigation of preclinical xylazine pharmacology. FDA also will work with industry sponsors and other federal government partners to support the development of treatments for xylazine-involved overdose and withdrawal. FDA stands ready to review Investigational New Drug applications utilizing the expedited review programs.

NIDA is supporting research on strategies to prevent and reduce harms from xylazine exposure. Given prior research showing that many people who use drugs try to avoid xylazine, one project focuses on engaging people who use opioids and seeking their input to inform effective harm reduction strategies.

Epidemiology Research (NIH)

NIDA is expanding research on the epidemiology of xylazine use that could help inform novel harm reduction and treatment interventions. For example, NIDA has solicited research on whether use of xylazine-adulterated drugs is changing over time and by geography, and whether other alpha-2 adrenergic agonists in addition to xylazine are emerging in the illicit drug supply. FDA is also funding research in this area.

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In June 2023, NIDA's Center for Clinical Trials Network convened stakeholders, clinical and scientific experts, and federal staff to provide their individual perspectives on potential best practices to treat people exposed to xylazine and mitigate harms; the proceedings have been published to help convey related research opportunities.[17] A current NIDA-funded project[18] focuses on understanding risk factors for xylazine wounds, their prevalence, barriers to wound care, and harm reduction practices to prevent severe wounds. NIDA-funded intramural and extramural researchers are also continuing preclinical studies to investigate the effects of xylazine and xylazine/opioids on respiratory function, withdrawal, and overdose risk, and potential overdose reversal agents specific for xylazine.

Research on Social Outcomes of Xylazine Use (NIH)

NIH's extramural funding supports rigorous research addressing Overdose Prevention Research Priorities. The current Extramural Research Project Opportunities emphasize evaluations of community-level substance use and overdose prevention strategies, strategies that link people with substance use disorders to recovery services, as well as research to understand polydrug use risk, patterns, and protective factors that prevent drug overdose and related harms, including those related to xylazine.

Department of Veterans Affairs Research and Development (VA)

VA's Office of Research and Development is a major funder of basic and applied research in the United States with an annual budget of $916 million. VA, per the FAAX Plan, has included in Funding Announcements support for treatment development, investigations of how xylazine impacts human physiology and behavior, research on social outcomes of xylazine use in humans, and research on use motivations. This work includes:

- Research to evaluate as quickly as possible potential xylazine antidotes in humans, and identify the most promising clinical stabilization, detoxification, and treatment protocols;
- Basic research on drug-drug interactions to understand the pharmacology, chemistry, biology, and toxicology of how xylazine and fentanyl interact in humans;
- Examination of varying effects across modes of xylazine administration (e.g., injecting, smoking, or inhalation);
- Effects of fentanyl adulterated with xylazine use during pregnancy;
- Population-level health, social, equity, and economic drivers and consequences of exposure to fentanyl adulterated with xylazine; and
- Research on awareness of and motivations for use of xylazine, strategies people use to reduce harm, how motivations related to use are changing over time, as well as the recovery process for those who have been able to stop use.

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Part IV: Conclusion

As the preceding sections of this report indicate, intensive work continues across the federal government and by its grantees to address the public health implications associated with the increasing presence of xylazine in the illicit drug supply, its potential exacerbation of opioid overdose and withdrawal, and its association with severe skin wounds. Over the past several months a great deal of information has been produced by federal and state agencies, as well as nonprofit organizations, to help understand the nature of the threat posed by xylazine and to inform our response. A clearinghouse[19] of this growing set of resources has been established at CDC for convenient access by medical professionals, harm reduction staff, researchers, government officials, and the general public.

The Biden-Harris Administration's work to implement the *FAAX Plan* will continue until the threat is fully addressed. The Administration appreciates Congress' continued interest and focus on this critical anti-drug priority.

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