

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. The 2021 Agricultural Proposed Rule as amended by this supplemental proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

We have developed a comprehensive Preliminary Economic Analysis of Impacts (PRIA) that assesses the impacts of the supplemental proposed rule (Ref. 1). We estimate costs and benefits of the 2021 agricultural water proposed rule in the “Standards for the Growing, Harvesting, Packing and Holding of Produce for Human Consumption Relating to Agricultural Water; Preliminary Regulatory Impact Analysis” (2021 agricultural water PRIA) (Ref. 2). This supplemental proposed rule makes no substantive changes to the provisions in the 2021 Agricultural Water Proposed Rule. Rather, this supplemental proposed rule proposes compliance dates for the pre-harvest agricultural water provisions for covered produce other than sprouts, which are not specified in the 2021 Agricultural Water Proposed Rule. The costs of the supplemental proposed rule are the costs of reading this rule. Annualized at either 3 percent or 7 percent, our primary estimates of this supplemental proposed rule are \$0.1 million. The benefit of this supplemental proposed rule is clarity to stakeholders about the proposed compliance dates for the pre-harvest agricultural water provisions for covered produce other than sprouts described in the 2021 agricultural water proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule and at <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.

VI. Analysis of Environmental Impact

The Agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The Agency’s finding of no

significant impact, including a supplement to the finding of no significant impact, and the evidence supporting that finding may be seen in the Dockets Management Staff (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday (Refs. 3 to 5). Under FDA’s regulations implementing the National Environmental Policy Act (21 CFR part 25), an action of this type would require an EA under 21 CFR 25.31a(a).

VII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this supplemental notice of proposed rulemaking contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

X. References

The following reference is on display at the Dockets Management Staff (see **ADDRESSES**) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <https://www.regulations.gov>. FDA has verified the website address, as of the date this document publishes in the **Federal**

Register, but websites are subject to change over time.

1. FDA, “Supplemental Notice of Proposed Rulemaking: Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water; Preliminary Regulatory Impact Analysis,” 2022. Available at: <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.
2. FDA, “Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water; Preliminary Regulatory Impact Analysis,” 2021. Available at: <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.
3. FDA, “Environmental Assessment for the Proposed Rule: Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water,” November 9, 2021.
4. FDA, “Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water: Finding of No Significant Impact,” November 9, 2021.
5. FDA, “Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water: Supplement to the Finding of No Significant Impact.”

Dated: July 11, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2022–15134 Filed 7–18–22; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–945]

Schedules of Controlled Substances: Removal of Fenfluramine From Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes to remove fenfluramine (chemical name: *N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts is possible, from the schedules of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which

requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. Fenfluramine is currently a schedule IV controlled substance. This action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule IV controlled substances, on persons who handle (manufacture, distribute, reverse distribute, import, export, dispense, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle fenfluramine.

DATES: Comments must be submitted electronically or postmarked, on or before August 18, 2022. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before August 18, 2022.

ADDRESSES: Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). The electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference "Docket No. DEA-945" on all electronic and written correspondence, including any attachments.

- **Electronic comments:** The Drug Enforcement Administration encourages commenters to submit all comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to <https://www.regulations.gov> and follow the on-line instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number. Submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have received a Comment Tracking Number, you have submitted your comment successfully and there is no need to resubmit the same comment.

Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

- **Paper comments:** Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu of* an electronic format, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701

Morrisette Drive, Springfield, Virginia 22152.

- **Hearing requests:** All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT:

Terrence L. Boos, Drug & Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. The Drug Enforcement Administration (DEA) will make comments available, unless reasonable cause is given, for public inspection online at <https://www.regulations.gov>. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want DEA to make it publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want DEA to make it publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

DEA will generally make available in publicly redacted form comments containing personal identifying information and confidential business information identified, as directed above. If a comment has so much confidential business information or personal identifying information that DEA cannot effectively redact it, DEA may not make all or part of that comment publicly available. Comments posted to <https://www.regulations.gov> may include any personal identifying information (such as name, address, and

phone number) included in the text of your electronic submission that is not identified as confidential as directed above.

An electronic copy of this document and supplemental information to this proposed rule are available at <https://www.regulations.gov> for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (5 U.S.C. 551-559). 21 CFR 1308.41-1308.45, and 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and such requests must include a statement of the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. 21 CFR 1316.47(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

Please note that, pursuant to 21 U.S.C. 811(a)(2), the purpose of a hearing would be to determine whether fenfluramine should be removed from the list of controlled substances based on a finding that the drug does not meet the requirements for inclusion in any schedule. All requests for hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information above.

Legal Authority

The Controlled Substances Act (CSA) provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated by the Attorney General (1) on his own motion, (2) at the request of the Secretary of the Department of Health and Human Services (HHS),¹ or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by a petition to remove fenfluramine from the list of scheduled controlled substances of the CSA, and is supported by, *inter alia*, a

¹ The Secretary of HHS has delegated to the Assistant Secretary for Health the authority to make domestic drug scheduling recommendations.

recommendation from the Assistant Secretary for Health of HHS and an evaluation of all relevant data by DEA. If finalized, this action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule IV controlled substances, on persons who handle or propose to handle fenfluramine.

Background

Fenfluramine (chemical name: *N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine), including its salts, isomers, and salts of such isomers, is currently controlled under 21 CFR 1308.14(d) as a schedule IV substance of the CSA. DEA placed fenfluramine in schedule IV on June 15, 1973 (38 FR 15719), after the U.S. Food and Drug Administration's (FDA) approval on June 14, 1973 of Pondimin, a fenfluramine product manufactured by Wyeth Pharmaceuticals, for the management of exogenous obesity. As noted in the HHS review of scientific and medical information, on September 25, 2019, Zogenix, Inc. (Zogenix; the Sponsor) submitted to FDA a New Drug Application (NDA) for Fintepla (fenfluramine),² for the treatment of seizures associated with Dravet syndrome (DS) in patients two years of age and older. (HHS, 2021) FDA approved the NDA on June 25, 2020, with the labelling listing fenfluramine as a schedule IV controlled substance.

On March 18, 1991, Interneuron Pharmaceuticals, Inc., the manufacturer of a fenfluramine product (dexfenfluramine, brand name Redux), petitioned DEA to decontrol fenfluramine. In response to DEA's request, HHS's Assistant Secretary for Health submitted to DEA a scientific and medical evaluation (HHS review) and a scheduling recommendation to DEA to decontrol fenfluramine on June 3, 1996. On May 6, 1997, DEA published a notice of proposed rulemaking (NPRM) in the **Federal Register** to remove fenfluramine from controls under the CSA. 62 FR 24620. On July 8, 1997, FDA issued a public health advisory regarding the use of fenfluramine, especially in conjunction with phentermine (schedule IV controlled substance) commonly known as "phen-fen," citing evidence of significant side effects associated with fenfluramine. FDA announced a voluntary withdrawal by the pharmaceutical manufacturers of

Pondimin (fenfluramine) and Redux (dexfenfluramine) from the U.S. market on September 15, 1997. HHS issued a final rule on March 8, 1999, listing drug products that were withdrawn or removed from the market because they were found to be unsafe or not effective, including fenfluramine hydrochloride. 64 FR 10944. On February 27, 2003, Indevus Pharmaceuticals, Inc., formerly known as Interneuron Pharmaceuticals, Inc., wrote to DEA to withdraw its petition to decontrol fenfluramine because it no longer markets fenfluramine products in the U.S. In light of the above-mentioned developments, on May 15, 2003, DEA withdrew the May 1997 NPRM. 68 FR 26247.

On October 18, 2018, Zogenix submitted to DEA a petition requesting that fenfluramine be removed from schedule IV of the CSA based on the data and rationale in DEA's May 1997 NPRM and more recent data collected, including data specific to Fintepla. The petition complied with the requirements of 21 CFR 1308.43(b) and DEA accepted the petition for filing on November 13, 2018.

Proposed Determination To Decontrol Fenfluramine

Pursuant to 21 U.S.C. 811(b), on September 22, 2020, DEA, having gathered the necessary data on fenfluramine, forwarded that data and the petition to HHS with a request for scientific and medical evaluation and scheduling recommendation for fenfluramine. On April 16, 2021, DEA received from HHS a scientific and medical evaluation conducted by FDA entitled "Basis for the recommendation to remove fenfluramine (*N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine) and its salts from all schedules of control under the Controlled Substances Act" and a scheduling recommendation. The National Institute on Drug Abuse (NIDA) concurred with the scientific and medical evaluation conducted by FDA. Based on the totality of the available scientific data, fenfluramine does not conform with the findings for schedule IV in 21 U.S.C. 812(b)(4) or in any other schedule as set forth in 21 U.S.C. 812(b). Based on FDA's scientific and medical review of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, HHS recommended that fenfluramine and its salts be removed from all schedules of the CSA.

The CSA requires DEA, as delegated by the Attorney General,³ to determine whether HHS's scientific and medical evaluation, scheduling recommendation, as well as all other relevant data constitute substantial evidence that a substance should be scheduled. 21 U.S.C. 811(b). DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, and all other relevant data, and completed its own eight-factor review document on fenfluramine pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in this proposal to remove fenfluramine from the schedules of the CSA. Both DEA and HHS analyses are available in their entirety under "Supporting and Related Material" of the public docket for this rule at <https://www.regulations.gov> under docket number DEA-945.

1. The Drug's Actual or Relative Potential for Abuse

The first factor DEA must consider is the actual or relative potential for abuse of fenfluramine. The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests the following points in determining whether a particular drug or substance has a potential for abuse:⁴

a. Whether there is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

As HHS noted, FDA approved fenfluramine (brand name Pondimin) in the U.S. on June 14, 1973, but FDA announced on September 15, 1997 that the pharmaceutical manufacturers of Pondimin and Redux (another FDA-approved fenfluramine product) voluntarily withdrew their products from the U.S. markets (see 68 FR 26247; May 15, 2003) after FDA issued a public health advisory in May 1997. FDA's public health advisory reported increased rates of cardiac valvulopathy and pulmonary arterial hypertension (PAH) related to fenfluramine use, particularly when used in the unapproved combination with phentermine for weight loss. On June 25, 2020, FDA approved Fintepla for the treatment of seizures associated with DS in patients two years of age and older. HHS noted in their scientific and

³ 28 CFR 0.100(b).

⁴ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4603.

² Fintepla is an oral solution that contains 2.2 mg/ml fenfluramine equivalent to 2.5 mg/ml of the hydrochloride salt.

medical evaluation that FDA reviewed the known hazards of fenfluramine and found no evidence of cardiac valvulopathy or PAH in pediatric DS patients treated with fenfluramine in the cardiovascular data the Petitioner submitted as part of their NDA application. FDA concluded that there is a reduced risk of cardiac valvulopathy or PAH due to the lower doses used to treat pediatric DS patients relative to the higher doses prescribed to obese adult patients. DEA notes that the FDA-approved labeling for Fintepla indicates that patients must be enrolled in the Fintepla risk evaluation and mitigation strategy (REMS) program and undergo cardiac monitoring before, during, and after treatment with fenfluramine to monitor for serious heart valve changes or high blood pressure in the arteries of the lungs.

b. Whether there is significant diversion of the drug or drugs containing such a substance from legitimate drug channels.

Fenfluramine was previously marketed in the U.S. from 1973 to 1997. According to DEA's forensic laboratory database System to Retrieve Information from Drug Evidence (STRIDE),⁵ 30 cases of fenfluramine were recorded between 1973 to 1991. Seven reports occurred in 1988 and involved seizures of fenfluramine from individuals traveling from Mexico into the U.S. Twenty-three drug seizure reports occurred after the manufacturers' voluntary withdrawal, in September 1997, of Pondimin and Redux from the U.S. market (1999 to 2009) in seven states and the District of Columbia. According to DEA's National Forensic Laboratory Information System-Drug (NFLIS-Drug),⁶ 177 seizures were reported from January 1997 to November 2021 in 30 states and the District of Columbia, with eight of the encounters reported from January 2017 through November 2021. In 169 of the encounters reported, fenfluramine was reported alone, with another encountered with only cellulose noted, a common filler or cutting agent. Fenfluramine was commonly

encountered as a powder, capsule, or tablet.

Additionally, DEA's May 1997 NPRM included data on fenfluramine from the Drug Abuse Warning Network (DAWN).⁷ (62 FR 24620, 24621) The DAWN data showed very little abuse, trafficking, and diversion of fenfluramine. In addition, HHS stated that there were no reports of diversion in clinical trials conducted by the current Petitioner.

c. Whether individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

The available evidence suggests that the prevalence of individuals taking fenfluramine on their own initiative, without advice from a licensed medical practitioner, does not occur to a meaningful degree.

d. Whether the drug or drugs containing such a substance are new drugs so related in their action to a substance already listed as having a potential for abuse to make it likely that it will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that they have a substantial capability of creating hazards to the health of the user or to the safety of the community.

According to HHS, fenfluramine is a serotonin (5-HT) releasing agent. Some drugs with the same mechanism of action are controlled in the CSA (e.g., 3,4-methylenedioxymethamphetamine or MDMA (also known as ecstasy, schedule I substance) and some are not. HHS further noted that in animal drug discrimination studies, which are generally sensitive to mechanisms of action, fenfluramine fully generalized to the discriminative stimulus effects of serotonergic substances such as MDMA, quipazine, and MK-212. The latter two are not controlled substances.

2. Scientific Evidence of the Drug's Pharmacological Effects, If Known

The binding and activity studies indicate that fenfluramine causes the release and prevents the reuptake of 5-HT; has antagonist activity at the beta-2 adrenergic receptor, the muscarinic M1 receptor, and the sodium ion

channel (hNav1.5); and has positive allosteric modulator activity at the nonspecific sigma-1 receptor.

Additionally, *d*-fenfluramine is a potent agonist of the 5-HT_{2B} receptor despite its weak binding affinity, has moderate agonist activity at the 5-HT_{2C} receptor, and has weak activity at the 5-HT_{2A} receptor, whereas *l*-norfenfluramine demonstrated moderate activity at the 5-HT_{2B} receptor and weak activity at the 5-HT_{2C} and 5-HT_{2A} receptors, respectively.

Drug discrimination assays in animals can be used to predict if a test drug will have abuse potential in humans. Although fenfluramine was first thought of as a stimulant based on its phenethylamine structure, fenfluramine does not generalize to stimulants when the discriminative stimulus effects were tested against a range of stimulant drugs. When rats were trained to discriminate fenfluramine from vehicle or other drugs, it became evident that fenfluramine produced discriminative stimulus effects similar to those of serotonergic substances such as quipazine and MK-212. HHS noted that fenfluramine fully generalized to drugs that do not have abuse potential such as lisuride, quipazine, and 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP), and generalized to some drugs that have abuse potential such as MDMA, but not to *para*-methoxyamphetamine (PMA, schedule I substance) or LSD (schedule I substance), which generalized to norfenfluramine. HHS concluded the drug discrimination studies are equivocal and do not provide clear evidence of the hallucinogenic effects of fenfluramine, a finding consistent with its clinical effects.

The reinforcing effects of fenfluramine, using various models and animal species, were also reviewed. HHS determined that the fenfluramine responded similarly to placebo and does not produce reinforcing effects. Further, HHS stated that these data are consistent with 5-HT agonists that are phenethylamines and lack stimulant activity. Fenfluramine is a phenethylamine that produces serotonergic agonist activity. Therefore, fenfluramine may be expected to produce placebo-like responding in these reinforcing assays.

According to HHS, after review of the published literature on the subjective effects of fenfluramine in humans, data indicate that single oral doses below 80 mg do not produce significant positive subjective effects. High doses ranging from 120 to 240 mg can produce positive subjective effects; however, the predominant effects at high doses were aversive and included sedation.

⁵ STRIDE reflects the results of drug evidence analyzed at DEA laboratories through September, 2014. STRIDE was queried on July 3, 2019.

⁶ NFLIS-Drug is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by local, State, and Federal forensic laboratories in the United States. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual State and local drug analysis cases. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS-Drug was queried on December 20, 2021. Some 2021 reports to NFLIS-Drug may still be pending.

⁷ DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments. DAWN was discontinued in 2011, but the Substance Abuse and Mental Health Services Administration's website currently indicates that it is re-establishing this system.

Anecdotal reports of abuse of fenfluramine from doctors exist; however, the published articles mention the subjects prefer other drugs. HHS mentioned that these effects are consistent with other measures indicating that subjects are tired, do not appreciate the psychoactive effects of fenfluramine, and do not “Want More” of the drug when asked.

HHS noted that Fintepla did not produce a concerning number of abuse-related adverse effects (AEs) after an analysis of the adverse effect profiles of all phases of development was completed. FDA reviewed the cardiovascular data submitted in the NDA for Fintepla and found no evidence of cardiac valvulopathy or PAH in pediatric DS patients treated with fenfluramine. The studies conducted for the NDA for Fintepla concluded that there was a reduced risk of cardiac valvulopathy or PAH because of the lower doses used to treat pediatric DS patients compared to the higher doses prescribed to obese adult patients.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

According to HHS, fenfluramine, also known by the developmental code ZX008, is the nonproprietary name of N-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine hydrochloride and is structurally similar to the amphetamine class of stimulants.

Fenfluramine has one asymmetric carbon and therefore may exist in two forms, which are identified as the (*d*) and the (*l*) enantiomers. Fenfluramine represents a mixture of both enantiomers. The molecular formula of fenfluramine hydrochloride (salt) is $C_{12}H_{16}F_3N$ HCl and the molecular weight is 267.72 g/mol. Fenfluramine is a white to off-white powder. Fenfluramine hydrochloride (salt) is soluble in organic solvents like ethanol (150 mg/mL) at 25 °C and dichloromethane (30–35 mg/mL) at 25 °C.

According to HHS, the development of fenfluramine (Fintepla) included a study that assessed the permeability of fenfluramine and norfenfluramine across Caco-2 cells that express P-glycoprotein (P-gp) transporters. P-gp transporters are known to actively transport foreign substances out of cells and the central nervous system (CNS) and can help determine a drug's permeability into the CNS. Both fenfluramine and norfenfluramine are highly permeable and the permeability was not affected by the P-gp antagonist valsopodar (10 μ M), suggesting

fenfluramine and norfenfluramine will pass easily into the CNS.

Pharmacokinetic data indicate that a single oral dose of fenfluramine (20 mg/kg, PO) in mice produced a C_{max} of 0.26 μ g/mL and an area under the curve (AUC) of 1.4 μ g/mL*hr, results similar to that of a 60 mg twice daily (BID) dose in healthy human adults. The same dose (20 mg/kg, PO) in rats produced a C_{max} of 0.36 μ g/mL and an AUC of 5.15 μ g/mL*hr, values higher than those in the mouse studies. The T_{max} of fenfluramine in rats ranged from 30 minutes to 2 hours, and the half-life was 2.5 hours.

According to HHS, the Sponsor of the Fintepla NDA provided pharmacokinetic data on norfenfluramine. In rats, a single oral dose of norfenfluramine is rapidly absorbed similarly to fenfluramine, with a T_{max} of 30 minutes and a half-life of 2.5 hours. Fenfluramine and norfenfluramine are easily distributed throughout the body and produced approximately 50 percent protein specific binding in human and rat plasma, however concentrations of both compounds were determined to be higher in the brain compared to the plasma, by 15 to 60-fold, depending on the study.

Fenfluramine is metabolized to norfenfluramine and is an active metabolite. Norfenfluramine and its *N*-oxygenation product were the only metabolites detected in liver S9 fractions in both rat and human samples. Fenfluramine and norfenfluramine are excreted primarily through the renal system (greater than 80%), with a small amount via the feces.

4. Its History and Current Pattern of Abuse

HHS noted that sporadic anecdotal reports of fenfluramine abuse were found when fenfluramine was marketed in the United States and Europe between 1963 and 1997. However, when compared to the large number of patients who were treated with and prescribed the drug during this time frame (approximately 55 million patients total, 50 million European patients with fenfluramine, and 5 million U.S. patients with fenfluramine or desfenfluramine), the number of people abusing fenfluramine is relatively small. According to these reports, HHS noted that these individuals either did not like fenfluramine because of its dysphoric effects or preferred another drug. Therefore, the history and current pattern of abuse of fenfluramine is low.

5. The Scope, Duration, and Significance of Abuse

HHS stated that the scope of abuse of fenfluramine was minimal when it was marketed and when compared to the number of patients to whom it was prescribed. According to HHS, fenfluramine, in most cases, was not the drug of choice to produce a psychoactive effect and was used only when no other drug was available. In most cases, a high dose fenfluramine⁸ produced a dysphoric effect leading the individual to stop taking fenfluramine.

DEA conducted a search of Federal, State, and local forensic laboratory databases such as NFLIS-Drug and STRIDE. The STRIDE database indicated that in the 18 years between 1973 and 1991, 30 cases of fenfluramine were entered into the database, and, there were 23 drug seizure reports during the period of 1999 to 2009 in seven states and the District of Columbia. According to NFLIS-Drug, there were 177 reports of fenfluramine from 30 states and the District of Columbia between January 1997 and November 2021. Eight of the 177 encounters were reported from January 2017 through November 2021 (1 in 2017, 3 in 2019, 3 in 2020, 1 in 2021). In 169 of these encounters, fenfluramine was reported alone. Another encounter was with only cellulose, a common filler or cutting agent. Fenfluramine was commonly encountered as a powder, capsule, or tablet.

HHS noted, as a result, the scope, duration, and significance of abuse of fenfluramine are minimal compared to the millions of patients who were prescribed and treated with the drug.

6. What, If Any, Risk There Is to the Public Health

Abuse potential of a drug is considered one indication of its risk to the public health. According to HHS, based on preclinical and clinical study data (see Factors 1 and 2), there are no signals that indicate that fenfluramine has abuse potential or that there is a risk to the public health from individuals abusing fenfluramine.

An FDA public health advisory, released on July 8, 1997, indicated increased rates of cardiac valvulopathy and PAH in relation to the use of fenfluramine, particularly in combination with phentermine. FDA approved Fintepla (fenfluramine) with a boxed warning on the label to address

⁸ The HHS review indicated that in human clinical studies and case reports, a single oral dose of 80 mg did not produce significant positive subjective effects; however, high single oral doses of 120 or 240 mg can produce positive subjective effects. Single oral doses over 80 mg were reported to be aversive and produce dysphoric effects.

the potential cardiac issues that have been correlated to the administration of fenfluramine and included language that patients would need to undergo cardiac assessments before, during, and after treatment with the drug.⁹

Thus, HHS concluded there is likely to be little risk to the public health from fenfluramine.

7. Its Psychic or Physiological Dependence Liability

The psychic dependence of fenfluramine was assessed in animal and clinical studies. HHS reported that fenfluramine failed to produce reinforcing effects in self-administration studies (Factor 2) and indicated that fenfluramine does not produce psychic dependence. HHS also noted there was a lack of psychic dependence in the clinical data discussed in Factors 2 and 4. These data indicate that fenfluramine produces dysphoric effects and that it is not the drug of choice among individuals with a drug use disorder. According to HHS, these data suggest that fenfluramine has low psychic dependence.

As per the physical dependence potential, there are reports of withdrawal syndrome upon cessation of fenfluramine use. HHS noted that a search of the FDA Adverse Event Reporting System (commonly known as FAERS) covering the years fenfluramine was marketed (1973 to 1997) produced four cases of “withdrawal syndrome” associated with fenfluramine. Physical dependence was not assessed in humans throughout the clinical development of fenfluramine (Fintepla). The Phase 1 studies were single dose studies or studies in which treatment was administered for only six days and not long enough to produce dependence. Additionally, physical dependence could not be assessed in the Phase 3 studies because the discontinuation of fenfluramine in seizure patients could not be done abruptly. The Phase 3 studies included a taper phase. The FDA-approved label recommends that fenfluramine be withdrawn gradually.

In conclusion, HHS noted that the psychic and physiologic dependence potential of fenfluramine is minimal in relation to the number of patients who have been treated with the drug. As a result, HHS stated that the number of reports of psychic and physiologic

dependence potential of fenfluramine is low.

8. Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA

Fenfluramine is not an immediate precursor of a substance already controlled under the CSA as defined by 21 U.S.C. 802(23).

Conclusion

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA’s consideration of its own eight-factor analysis, the Administrator of DEA (Administrator), pursuant to 21 U.S.C. 811(a) and (c), finds that these facts and all relevant data demonstrate that fenfluramine does not meet the requirements under 21 U.S.C. 812(b) for inclusion in any schedule, and should be removed from control under the CSA. Specifically, the Administrator finds the following:

(1) Fenfluramine appears to have no potential for abuse. According to HHS, the profile of activity for fenfluramine differs from other 5-HT agonists that are phenethylamines as it does not generalize to a stimulant. In addition, the *in vitro*, animal, human, and epidemiology data indicate that fenfluramine has no potential for abuse.

(2) Fenfluramine has a currently accepted medical use in treatment in the United States. FDA approved the NDA for Fintepla (fenfluramine) on June 25, 2020 for the treatment of DS in patients aged two years and older.

(3) Fenfluramine does not appear to have psychological or physical dependence liability. According to HHS, the reports of psychic or physiologic dependence of fenfluramine are minimal when viewed in the context of large number of patients who were treated with the drug in the United States and Europe between 1963 and 1997. Thus, the psychic and physiological dependence liability of fenfluramine is lower than that of substances in schedules IV and V.

Based on these findings, the Administrator concludes that fenfluramine does not meet the requirements for inclusion in any schedule and should be removed from control under the CSA.

Regulatory Analyses

Executive Orders 12866 (Regulatory Planning and Review) and 13563 (Improving Regulation and Regulatory Review)

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is

subject to formal rulemaking procedures done “on the record after opportunity for a hearing,” which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for removing a drug or other substance from the list of controlled substances. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the National Government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This proposed rule does not have tribal implications warranting the application of E.O. 13175. This proposed rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove fenfluramine from the list of schedules of the CSA. This action will remove regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances for handlers and proposed handlers of fenfluramine. Accordingly, it has the potential for some economic impact in the form of cost savings.

⁹DEA notes that this boxed warning also states that Fintepla is available only through a restricted program, Fintepla REMS. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=400>.

If finalized, the proposed rule will affect all persons who would handle, or propose to handle fenfluramine. Fenfluramine as a pharmaceutical product (Fintepla) is currently available and marketed in the U.S. Because fenfluramine is currently a schedule IV drug, all legal handling of fenfluramine is currently done under appropriate DEA license. In such instances, DEA's knowledge of its registrant population forms the basis for estimating the number of affected entities and small entities that are affected by this rulemaking. There are currently 40 unique registrations authorized to handle fenfluramine specifically, as well as a number of registered analytical labs that are authorized to handle schedule IV controlled substances generally. From review of entity names, DEA estimates these 40 registrations represent 27 entities. Some of these entities are likely to be small entities. However, since DEA does not have information of registrant size and the majority of DEA registrants are small entities or are employed by small entities, DEA estimates a maximum of 27 entities are small entities. Therefore, DEA conservatively estimates as many as 27 small entities are affected by this proposed rule. However, because this rule would remove fenfluramine from regulatory controls of the CSA, it is likely to result in some cost savings. Any person planning to handle fenfluramine will realize cost savings in the form of saved DEA registration fees, and the elimination of physical security, recordkeeping, and reporting requirements. Because of these factors, DEA projects that this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, DEA has determined pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995, (2 U.S.C. 1501 *et seq.*), that this proposed action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any 1 year. . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This proposed action does not impose a new collection of information requirement under the Paperwork

Reduction Act of 1995. (44 U.S.C. 3501–3521).

Signing Authority

This document of the Drug Enforcement Administration was signed on July 13, 2022, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the **Federal Register**.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA proposes to amend 21 CFR part 1308 as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

§ 1308.14 [Amended]

- 2. In § 1308.14, remove and reserve paragraph (d).

Scott Brinks,

Federal Register Liaison Officer, Drug Enforcement Administration.

[FR Doc. 2022–15335 Filed 7–18–22; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[Docket Number USCG–2022–0595]

RIN 1625–AA00

Safety Zone; Ironman Michigan, Frankfort Harbor, MI

AGENCY: Coast Guard, DHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Coast Guard is proposing to establish a temporary safety zone for certain waters of Betsie Lake in Frankfort, MI. This action is necessary

to provide for the safety of life on these navigable waters during the swim portion of an Ironman event on September 11, 2022. This proposed rulemaking would restrict usage by persons and vessels within the safety zone. At no time during the effective period may vessels transit the waters of Betsie Lake in the vicinity of a triangular shaped race course enclosed by the following three coordinates: 44°37.80' N, –086°13.91' W to 44°37.81' N, –086°14.22' W to 44°37.58' N, –086°13.75' W, then back to the starting point. The race course will be marked by buoys. These restrictions would apply to all persons and vessels during the effective period unless authorized by the Captain of the Port Lake Michigan or a designated representative. We invite your comments on this proposed rulemaking.

DATES: Comments and related material must be received by the Coast Guard on or before August 18, 2022.

ADDRESSES: You may submit comments identified by docket number USCG–2022–0595 using the Federal eRulemaking Portal at <https://www.regulations.gov>. See the "Public Participation and Request for Comments" portion of the **SUPPLEMENTARY INFORMATION** section for further instructions on submitting comments.

FOR FURTHER INFORMATION CONTACT: If you have questions about this proposed rulemaking, call or email Chief Petty Officer Jeromy Sherrill, Sector Lake Michigan Waterways Management Division, U.S. Coast Guard; telephone 414–747–7148, email Jeromy.N.Sherrill@uscg.mil.

SUPPLEMENTARY INFORMATION:

I. Table of Abbreviations

CFR Code of Federal Regulations
DHS Department of Homeland Security
FR Federal Register
NPRM Notice of proposed rulemaking
§ Section
U.S.C. United States Code

On June 23, 2022, the Coast Guard was notified by the event sponsor of its intent to host Ironman Michigan in Frankfort, MI on September 11, 2022 from 8:00 a.m. to 10:15 a.m. The swim will begin near Frankfort Municipal Marina in Betsie Lake. The race course will be triangular shaped area enclosed by the following coordinates: 44°37.80' N, –086°13.91' W to 44°37.81' N, –086°14.22' W to 44°37.58' N, –086°13.75' W, then back to the starting point. The race course will be marked by buoys. The COTP has determined that potential hazards associated with the triathlon would be