9/6/17

The following information is being provided pursuant to the requirements of Executive Order 2011-01K and Senate Bill 2 of the 129th General Assembly, which require state agencies, including the State of Ohio Board of Pharmacy, to draft rules in collaboration with stakeholders, assess and justify an adverse impact on the business community (as defined by S.B. 2), and provide an opportunity for the affected public to provide input on the following rule.

Amended Rule

- **4729-11-02:** Classifies Etizolam as a Schedule I controlled substance.

Comments on the proposed rules will be accepted until close of business on September 22, 2017. Please send all comments to the following email address:
Cameron.mcnamee@pharmacy.ohio.gov

In addition, please copy your comments to:
CSIPublicComments@governor.ohio.gov

CSI - Ohio
The Common Sense Initiative

Business Impact Analysis

Agency Name: State of Ohio Board of Pharmacy

Regulation/Package Title: Etizolam

Rule Number(s): Amended: 4729-11-02

Date: 9/06/2017

Rule Type:

New	5-Year Review
Amended	Rescinded

The Common Sense Initiative was established by Executive Order 2011-01K and placed within the Office of the Lieutenant Governor. Under the CSI Initiative, agencies should balance the critical objectives of all regulations with the costs of compliance by the regulated parties. Agencies should promote transparency, consistency, predictability, and flexibility in regulatory activities. Agencies should prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.

Regulatory Intent

1. Please briefly describe the draft regulation in plain language.

Amended Rules

- **4729-11-02:** Classifies Etizolam as a Schedule I controlled substance.

2. Please list the Ohio statute authorizing the Agency to adopt this regulation.

The proposed rule is authorized by sections 4729.26 and 3719.28 of the Ohio Revised Code. The following sections of the Ohio Revised Code are also considered authorizing statutes for this rule package: 3719.44.

3. **Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program?**

The rule does not implement a federal requirement.

4. **If the regulation includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.**

It is known that as opioid abuse has continued to rise, so too has the prevalence of benzodiazepine abuse, including etizolam. Reports indicate that 30 percent of fatal overdose deaths involving opioids also involve benzodiazepines. Etizolam abuse is likely to continue to grow without effective counter-control measures.

By scheduling such drugs that are not approved by the FDA, the Board hopes to reduce access to the supply of these potentially lethal substances and assist law enforcement is prosecuting individuals trafficking in these drugs.

5. **What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?**

Section 4729.26 and 3719.28 of the Ohio Revised Code authorizes the state board of pharmacy to adopt rules governing dangerous drugs, including controlled substances.

The abuse of etizolam in conjunction with opioids presents a significant public health risk. Etizolam is 10 times more potent than diazepam and potentiates opioid respiratory depression.

6. **How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?**

The success of the regulation will be measured by having a rule written in plain language that can be utilized by law enforcement.

Development of the Regulation

7. **Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.**

Board staff consulted with Ohio crime labs as well as regulators in other states. As detailed in the Board's scheduling resolution (included at the end of this document), Etizolam remains

unscheduled in the United States and its abuse is growing. Consequently, it has been scheduled in several other states including Kansas, Mississippi, and Virginia, among others.

8. What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?

Any proposed feedback provided by Ohio crime labs and regulators in other states was incorporated into the rule package and scheduling resolution.

9. What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?

After a thorough review of all available data, the Board found that that Etizolam:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision; and
4. Poses a risk to the public health of the citizens in this state.

The supporting data is included in the Board's scheduling resolution that is included with this document.

10. What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn't the Agency consider regulatory alternatives?

As the regulation is essential to protecting the public's safety by ensuring uniform rules for controlled substances, the State of Ohio Board of Pharmacy did not consider any regulatory alternatives.

11. Did the Agency specifically consider a performance-based regulation? Please explain. ***Performance-based regulations define the required outcome, but don't dictate the process the regulated stakeholders must use to achieve compliance.***

The Board did not consider a performance-based regulation for the rule in this package. It is the Board's responsibility to ensure that regulations are consistent throughout the state. It was the determination of the Board that the rule package did not lend itself to performance-based regulations.

12. What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?

The Board of Pharmacy's Senior Legal Counsel reviewed existing rules to ensure that the proposed rule does not duplicate another State of Ohio Board of Pharmacy regulation.

13. Please describe the Agency's plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.

The rule will be posted on the Pharmacy Board's web site and notices will be sent to associations, individuals and groups. Pharmacy Board staff are also available via phone or email to answer questions regarding implementation of the rule.

Adverse Impact to Business

14. Provide a summary of the estimated cost of compliance with the rule. Specifically, please do the following:

a. Identify the scope of the impacted business community;

Individuals possessing Etizolam. NOTE: Research and other approved labs are lawfully able to possess schedule I controlled substances with valid licensure from the DEA and the Board of Pharmacy.

b. Identify the nature of the adverse impact (e.g., license fees, fines, employer time for compliance); and

Violation of these rules would result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.

c. Quantify the expected adverse impact from the regulation.

- **4729-11-02:** This should not have any adverse impact on business, as it is intended to target a drug that has not been approved by the FDA and has no current medical use.

Regulatory Flexibility

15. Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?

After a thorough review of all available data, the Board found that that Etizolam:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision; and
4. Poses a risk to the public health of the citizens in this state.

The supporting data is included in the Board's scheduling resolution that is included with this document.

16. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.

This rule does not provide any exemptions or alternative means of compliance for small businesses. The law does not differentiate on the size of the business and therefore the regulation is uniform across Ohio.

17. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?

The State of Ohio Board of Pharmacy does not fine licensees or impose penalties for first-time paperwork violations. However, any failure of a standard of care in the practice of pharmacy is not considered a paperwork error but a quality assurance issue by the licensee that is necessary for the protection of the public.

18. What resources are available to assist small businesses with compliance of the regulation?

Board of Pharmacy staff is available by telephone and e-mail to answer questions. Board staff members also provide presentations to groups and associations who seek updates on current regulations.

4729-11-02 Schedule I controlled substances.

(A) The state board of pharmacy hereby schedules the following synthetic cannabinoid compounds as schedule I controlled substance hallucinogens:

(1) PB-22 (chemical name: quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate) ;

(2) 5-Fluoro-PB-22 (chemical name: quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate).

(B) Except as otherwise provided in section 3719.41 of the Revised Code, any compound that meets at least three of the following pharmacophore requirements to bind at the CB1 and CB2 receptors, as identified by a report from an established forensic laboratory, is a schedule I controlled substance hallucinogen:

(1) A chemical scaffold consisting of substituted or non-substituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles or other ring types);

(2) Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors;

(3) Carbonyl or ester or equivalent for hydrogen bonding;

(4) Cyclohexane, naphthalene ring, substituted butanamide or equivalent for steric requirements for CB1 and CB2 receptor binding.

(C) Except as otherwise provided in section 3719.41 of the Revised Code, any compound that contains the structural requirements of the cathinone pharmacophore, as identified by a report from an established forensic laboratory, is a schedule I controlled substance.

(D) Except as otherwise provided in section 3719.41 of the Revised Code, any compound that meets the following fentanyl pharmacophore requirements to bind at the mu receptor, as identified by a report from an established forensic laboratory, is a schedule I controlled substance opiate:

(1) A chemical scaffold consisting of:

(a) A five, six or seven member ring structure containing a nitrogen, whether or not further substituted; and

(b) An attached nitrogen to the ring, whether or not that nitrogen is enclosed in a ring structure, including an attached aromatic ring or other lipophilic group to that nitrogen;

(2) A polar functional group attached to the chemical scaffold, including but not limited to, a hydroxyl, ketone, amide or ester;

(3) An alkyl or aryl substitution off the ring nitrogen of the chemical scaffold; and

(4) The compound has not been approved for medical use by the United States food and drug administration.

(E) 6-monoacetylmorphine (6-MAM) is a schedule I controlled substance opium derivative.

(F) 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-benzamide (U-47700) is a schedule I controlled substance opium derivative.

(G) Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine) is a schedule I controlled substance depressant.

Steven W. Schierholt, Esq.
Executive Director

John R. Kasich
Governor

STATE OF OHIO BOARD OF PHARMACY

A RESOLUTION

Section 1: Summary

The State of Ohio Board of Pharmacy (BOP), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the following into Schedule I:

Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine), as a depressant.

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluating Etizolam Under the Eight Criteria

(1) The actual or relative potential for abuse.

The scientific evidence included in this report will illustrate that Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine) has a pharmacological profile similar to that of classical benzodiazepines. Despite being available as a prescription anxiolytic in Japan, India, and Italy, Etizolam is not approved for medicinal purposes in the United States and Europe. Because it is not controlled nationally in the United States, Etizolam is often promoted as a legal means of achieving the same effects as its scheduled benzodiazepine counterparts.

Actual abuse of Etizolam has been documented in Europe, India, and in the United States. Observed trends prompted scheduling action in Alabama (schedule I), Arkansas (schedule I), Georgia (schedule IV), Kansas (schedule I), Mississippi (schedule I), and Virginia (schedule I).

Responses from Ohio crime labs queried while preparing this report illustrate that Etizolam abuse is seen across Ohio. Like other non-controlled substances, however, quantifying the actual abuse is elusive. Laboratories either do not target their analysis for the identification of the non-controlled substance or the reported findings are, "no controlled substance found."

Gupta S, Garg B. A case of etizolam dependence. Indian J. of Pharmacology; 46(6): 655–656 (2014).

Liveri K, Constantinou MA, Afxentiou M, Kanari P. A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus. Forensic Science Int. 265: 160–165 (2016).

Sanna, E. et al. Low tolerance and dependence liabilities of etizolam: Molecular, functional, and pharmacological correlates. European J. of Pharmacology; 519(1–2): 31–42 (2005).

(2) The scientific evidence of the pharmacological effect of the substance.

Liveri and others (2016) provide that Etizolam is 10 times more potent than diazepam. The pharmacological effects of benzodiazepines have become a growing concern during the opioid crisis because they potentiate the respiratory depressant effect of opioids. Sun and others (2017) report that 30 percent of fatal overdose deaths involving opioids also involve benzodiazepines.

Liveri K, Constantinou MA, Afxentiou M, Kanari P. A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus. Forensic Science Int. 265: 160–165 (2016).

Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 356:j760 (available at https://doi.org/10.1136/bmj.j760) (2017).

(3) The state of current scientific knowledge regarding the substance.

Etizolam originates from research completed by Tahari (1978).

Etizolam is moderately well characterized by both the general chemistry, medical and forensic communities.

Tahari T, et al. Syntheses and structure-activity relationships of 6-Aryl-4H-s-triazolo[3,4-c]thieno[2,3-e][1,4]diazepines. Arzneimittel-Formschung 28:1153–1158 (1978).

(4) The history and current pattern of abuse.

In 1983, Etizolam was introduced as a prescription drug in Japan. Its historic reputation as a safe drug with low potential for abuse contributed to Etizolam being widely prescribed for the treatment of anxiety and for its muscle-relaxing properties.

Since that time, however, the types of benzodiazepines and the way the class is promoted has changed. In a similar modus operandi as witnessed in the case of synthetic cannabinoids and substituted cathinones, substances sold as "designer benzodiazepines"—including Etizolam—are widely available on the internet as alternatives to prescription-only benzodiazepines. As the opioid crisis has evolved, iatrogenic comorbidity involving benzodiazepines and opioids has become a growing concern.

Liveri K, Constantinou MA, Afxentiou M, Kanari P. A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus. Forensic Science Int. 265: 160–165 (2016).

Nakamae T, et al. Case report: Etizolam and its major metabolites in two unnatural death cases. Forensic Science Int. 182: e1–e6(2008).

Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 356:j760 (available at https://doi.org/10.1136/bmj.j760) (2017).

Hoiseth G, Tuv SS, Karinen R. Blood concentrations of new designer benzodiazepines in forensic cases. Forensic Science Int 268: 35–38 (2016).

(5) The scope, duration, and significance of abuse.

Like other non-controlled substances, precisely determining the scope of abuse is a challenge. Laboratories either do not target their analysis for the identification of the non-controlled substance or the reported findings are, "no controlled substance found."

Nonetheless, it is known that as opioid abuse has continued to rise, so too has the prevalence of benzodiazepine abuse, including etizolam. Sun and others (2017) report that 30 percent of fatal overdose deaths involving opioids also involve benzodiazepines. Etizolam abuse is likely to continue to grow without effective counter-control measures.

Drug Fact Sheet: Etizolam. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/drug_chem_info/etizolam.pdf) (2014).
Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 356:j760 (available at https://doi.org/10.1136/bmj.j760) (2017).

(6) The risk to the public health.

The abuse of etizolam in conjunction with opioids presents a significant public health risk. Etizolam is 10 times more potent than diazepam and potentiates opioid respiratory depression.

(7) The potential of the substance to produce psychic or physiological dependence liability; and

Though reported by Sanna (2005) to have a lower tolerance and dependence liability than other benzodiazepines, Etizolam is a GABA chloride channel agonist. Like other such agonists, Gupta (2014) reports that Etizolam can produce psychological and physiological addiction that is difficult to treat.

Gupta S, Garg B. A case of etizolam dependence. Indian J. of Pharmacology; 46(6): 655–656 (2014).

Sanna, E. et al. Low tolerance and dependence liabilities of etizolam: Molecular, functional, and pharmacological correlates. European J. of Pharmacology; 519(1–2): 31–42 (2005).

(8) Whether the substance is an immediate precursor.

Etizolam is not known to be an immediate precursor.

Section 5: Finding of the Board

Section 3719.44 of the Ohio Revised Code authorizes that the State of Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a thorough review of all available data, the State of Ohio Board of Pharmacy finds that Etizolam:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision; and

4. Poses a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that Etizolam be controlled in Schedule I and authorizes the filing of amended rule 4729-11-02 of the Administrative Code that was approved on August/8/2017.