

**2013 HOUSE JUDICIARY**

**HB 1070**

# 2013 HOUSE STANDING COMMITTEE MINUTES

House Judiciary Committee  
Prairie Room, State Capitol

HB 1070  
January 14, 2013  
Job #17167

Conference Committee

Committee Clerk Signature



## Explanation or reason for introduction of bill/resolution:

Relating to the scheduling of controlled substances.

## Minutes:

Testimony # 1,2,3,4,5

**Chairman Koppelman:** Opened the hearing on HB 1070.

**Mark Hardy, Assistant Executive Director of the ND State Board of Pharmacy:** (See testimony #1 and 2) He went over these handouts.

**Rep. Klemin:** I don't see an emergency clause in the bill and there is none in the amendment. Did I miss it?

**Mark Hardy:** I want to put an emergency clause on the bill.

**Rep. Klemin:** I think you have to have another section at the end of the bill saying this is an emergency.

**Rep. Kretschmar:** How often do these new drugs come out and should be on it?

**Mark Hardy:** As far as the schedule 1 substances; it is a revolving door and we are always trying to stay in front of what the chemists and what the drug makers are doing. As far as schedule 2 through 5; it is a continuous thing through the DEA. When it becomes a federally controlled substance it takes precedence.

**Rep. Larson:** You have not been aware of the bill I was sponsoring regarding synthetic drugs yet?

**Mark Hardy:** No. The Attorney General briefed me on the Bill #1133.

**Rep. Larson:** The reason for my bill is not get into all of the pharmaceutical names of the chemicals, but anybody that possess or manufacturers a analog in order to try and copy these drugs would be guilty of those offences without having to know the specific chemical compound that might be morphed by unscrupulous people trying to see these products. Part of the problem with these specific drugs is time at the crime lab when law enforcement

does come across some of these chemicals then they have to send them to the lab to find out if this is one that is listed in the schedule. Do you know how long it takes at this point for that testing to be done?

**Mark Hardy:** I think Char Schweitzer of the Crime Law can answer that as well. That approach is something we certainly would support.

**Rep. Larson:** I also think this is a great step that needs to happen. I just would like to make sure that our bills work together. I would like to continue the discussion when the other bill comes up for debate.

**Mark Hardy:** I will take a look at your bill and discuss it with you.

**Wayne Stenhjem, Attorney General of ND:** Synthetic drug abuse has exploded in ND the last four years which presents many challenges for law enforcement and prosecutors. In 2011 the legislature scheduled seven chemical groups with synthetic cannabinoids which were being sold as incense and several synthetic cannabinoids which were being sold as bath salts. The substances were being sold as legal alternatives to controlled substances. Despite their labels stating that their products were "not for human consumption" the substances are smoked, snorted and ingested for the purpose of getting high. I have some samples that we received around ND and you will see most of them are brightly packaged because they are likely to appeal to younger people; even though they say they are not intended for human consumption. Some of the newer compounds have never been researched or studied on human or users are test subjects each time they ingest one of these substances. Two years ago we thought we had taken care of the problem; however the manufacturers of these substances changed the chemical structure making the new substances similar to but different from the chemical classes that had been controlled. Law enforcement, prosecutors and medical providers began to see the same products labeled with new names such as new dimension spark 100% pure evil now containing a non-controlled synthetic. Reports are coming in of junior overdosing on very small amounts of these substances. People who were smoking them were combated with police. Users told police they thought they were having a heart attack. They thought their hearts were going to jump out of their chests. Police have also been to hospital emergency rooms where users have been foaming at the mouth and were incoherent. In June 2012 in Grand Forks area two teenagers and at least one other individual overdosed on a synthetic cannabinoid known as 2BI with the street name of smiles. In that case witnesses described the victims as thrashing about and growling and one of the victims was pounding his head in the ground before he stopped breathing. We have no way under the law to prohibit those dealers from selling those new substances. These substances had fallen through the cracks of our statues and the Grand Forks case with the distribution of 2CI resulted in the death of two teenagers. The federal government was able to charge the distributors of Smiles with drug trafficking offences. DEA confirmed that the new synthetic antinodes available since our law were passed including XLR 11. ND needs a controlled substance antinodes statue so law enforcement are able to stop the distribution of substances that are similar to controlled, yet different enough to be legal. One of the consumers used a pipe to smoke the New Dimension and reported that smoking the product gives him euphoric relief. The second consumer smoked the product in a joint and reported to law enforcement gave him a buzz. The second consumer also allowed another person to smoke some of that

joint and shortly thereafter this 21 year old male called 911 in distress and complaining that he felt this heart was going to explode. The sale of street drugs has had a damaging effect on public health here in ND and elsewhere. These drugs are known to cause serious health effects like extreme nervousness, nausea and vomiting, fast racing heart, paranoia and sometimes death. Over the last several years there has been a large increase in emergency room calls and patients being brought to emergency rooms resulting from ingesting or inhaling those alternatives. That causes a big problem with people who are on patrol or probation and as a condition of this are not to be using mind altering substances, but you can't detect these so they are using them. Working with the Board of Pharmacy my office drafted this proposed legislation, but before we could not wait until the legislature meet and that is why the Board of Pharmacy adopted as emergency rules pretty much the same enactment that you see before us. (See handouts 3 & 4). To answer the question that Rep. Larson had. Here is what we are seeing in the Crime Lab; this is the chart. In 2009 when we started to see the synthetic drugs come along we had 10 of them. By 2012 we are up to 1,470 samples that these synthetics that were submitted. The problem with these samples is they differ from marijuana which is very easy and quick to analyze. It takes quite a while to actually to sort through these drugs. The example #4 is a list of the 25 most used drugs that are reported for use. Went over the form from top to bottom. The ones you are not familiar with are the synthetics that we are hoping to ban.

**Rep. Brabandt:** These samples that were passed around; where are they manufactured and packaged?

**Wayne Stenehjem:** They can be manufactured and packaged anywhere. Many of those substances come from China, Indonesia, or somewhere overseas. They may be packaged in California or maybe overseas and they come here and are sold. The head shops in ND I have issued a cease and desist.

**Rep. Paur:** These bath salts come up with a chemical name and then make it illegal or similar compounds and then let the courts decide if it falls under.

**Wayne Stenehjem:** This bill is designed to do exactly that for all of these known core chemicals that we are aware of. There may be another whole core of substances that come along and without getting in to Rep. Larson's bill that is what that bill is designed to deal with. I think the bill you have in front of you will cover the changes that might be made to the substances that we have listed that we are aware of and Rep. Larson's bill will cover the rest of anything else that might come along.

**Chair. Koppelman:** We will be holding this bill so that we hear the other bill too before we take action so they are in harmony.

**Rep. Maragos:** In this top 25 list this is just samples of drugs.

**Wayne Stenehjem:** All kids across the US are using these substances. Part of the reason they do this is they are packaging and using it and I beg for your action and I appreciate your attention and interest in this legislation.

**Charlene Schweitzer, Forensic Scientist from the State Crime Lab:** (See testimony #5). She read her testimony.

**Rep. Brabandt:** I noticed on those packages that were sent around there was a list of ingredients on the back. How accurate is that list of ingredients?

**Charlene Schweitzer:** The ingredients are not accurate at all because the chemicals that I test for and finding are not listed on those at all. What is listed is what that plant material may or may not be and we don't even confirm what the plant material is. It is the chemical that is sprayed on that plant material so from my point of view they are not accurate at all.

**Rep. Brabandt:** How many known packaged products are now on the market?

**Charlene Schweitzer:** There are 100's if not 1,000's.

**Rep. Hanson:** If they are not accurate to what is in the actual product how they are able to be sold legally now?

**Charlene Schweitzer:** That disclaimer that they had on not breaking the consumption is the loop hole that they use so the FDA cannot get involved.

**Rep. Hanson:** They cannot get caught for that even though they are not legal?

**Charlene Schweitzer:** That is how your cease and desist order works where they weren't actually saying what actually was in there. It has been an ongoing battle they last few years.

**Rep. Hogan:** Is the use of synthetic drugs significant in all parts of the state.

**Charlene Schweitzer:** I would say yes it is all over; not just in North Dakota, but is a worldwide problem.

**Rep. Koppelman:** Is the sale in the rural areas as well or primary in the urban centers?

**Charlene Schweitzer:** I would say it is primary in the urban centers where these shops are so that is why we were trying to shut those places down because kids that were under 18 could walk in and purchase these. Stopping the internet is going to be a whole nether battle.

Opposition: None

Neutral: None

**Rep. Koppelman:** As you heard in the testimony this has been a difficult issue to get our hands around because of the changing definitions. We attempted to do something like this in the legislature before as did the board of pharmacy. The board runs into a legal snag. You all know about government regulation etc. The Board of Pharmacy was able to craft an emergency rule to attempt to stop these a few years ago and it was struck down by a

court because the finding was that the notice in the rule making was not sufficient. The language describing the rule was pretty open so at the last session we made more specific the requirement of who needs to be notified when emergency rules are made and that is what allowed the board this time to do that and overcome the problem. The newly elected Senator Howard Anderson is actually is head of the Board of Pharmacy who he works with.

**Rep. Larson:** I did not get my question answered about the crime lab, how long it takes to exam something that is put in to the crime lab. I think this holds people in jail that clogs the jails.

**Charlene Schweitzer:** That is a great question. These synthetic drugs have had a great impact on our caseload because there are no field tests and these compounds keep changing and officers can't make identification so it is hard for them to even know if they can charge anybody or not. For a while we got bombarded and our turnaround time was two months. Now we have put in some extra hours and got an extra intern so we are down to about a month before we can get testing back to the agencies. The actual testing of this stuff can take a long time if it is something new. We have to seek out a standard and a lot of these chemical companies can't keep up the standard that the forensic community needs because these compounds keep changing to rapidly. We have to have the DEA community lab sanitizes a standard for us. I cannot give you a definite number but it does take some time.

**Wayne Stenehjem:** The governor has recommended an additional staff person at the crime lab and that is driven largely due to the synthetic issue. That will be heard on the floor tomorrow and that is one of the important components of the budget.

**Rep. Paur:** These synthetic packaged drugs say they are not for human consumption and people get high over them. People have been getting high from glue; from gasoline; they are not for human consumption. Where does the break line come in between to what is being abused but has a legitimate purpose?

**Wayne Stenehjem:** Those substances for schedule one are the substances that have no known medical or other use. The glue has another excepted and beneficial use for society where these don't. We might have legislation that already deals with some of this because we do have a statue that covers people who intentionally inhale airplane glue for example. It is a serious public health issue and that is why I think it is important that you enact this Legislation.

**Rep. Larson:** Bath salts smell like dirty feet so: I am not exactly sure why anyone would like to soak in those.

**Wayne Stenehjem:** It is well know that that is not what they are for.

**Rep. Koppelman:** I think in reply to Rep. Larson it is questioning the misuse of something that has another legitimate purpose versus something that has none.

Hearing closed.

# 2013 HOUSE STANDING COMMITTEE MINUTES

House Judiciary Committee  
Prairie Room, State Capitol

HB 1070  
January 23, 2013  
Job 17625

Conference Committee

*Kristie Hetzler*

## Explanation or reason for introduction of bill/resolution:

Relating to the scheduling of controlled substances.

## Minutes:

**Chairman Koppelman:** Opens.

**Rep Delmore:** I believe there is to be an amendment, an emergency clause added to this so that it goes into effect and start protecting people.

**Chairman Koppelman:** You are correct and there was a suggested amendment distributed and it came from the Board of Pharmacy. We can move on it now however we don't have the amendment drafted out in front of us but legislative counsel is aware of it and if we all know what the emergency clause (defines it) is we can go forward.

**Rep Delmore:** Moved amendment to HB 1070 from the Board of Pharmacy with the necessary additional language to add the emergency clause.

**Rep Larson:** Second.

Discussion:

**Rep Steiner:** Are we going to combine this with the other bill.

**Chairman Koppelman:** Both bills are harmonized and work hand and glove. Vote on amendments.

**Yah:** 12

**Nay:** 0

**Absent:** 2

**Chairman Koppelman:** Motion carries the bill is amended.

**Rep Toman:** Motion Do Pass.

**Rep Delmore:** Seconds.

**Yes:** 12

**No:** 0

**Absent:** 2

**Chairman Koppelman:** Closes.

**Carried by:** Rep Larson.

January 24, 2013

1/24/13  
JSC  
10/2

PROPOSED AMENDMENTS TO HOUSE BILL NO. 1070

Page 1, line 3, after "substances" insert "; and to declare an emergency"

Page 11, line 11, after "system" insert "; or"

Page 11, line 20, after the underscored comma insert "methylenedioxybenzyl."

Page 25, line 18, after "dd." insert "Lorcaserin."

ee."

Page 25, line 19, overstrike "ee." and insert immediately thereafter "ff."

Page 25, line 20, overstrike "ff." and insert immediately thereafter "gg."

Page 25, line 21, overstrike "gg." and insert immediately thereafter "hh."

Page 25, line 22, overstrike "hh." and insert immediately thereafter "ii."

Page 25, line 23, overstrike "ii." and insert immediately thereafter "jj."

Page 25, line 24, overstrike "jj." and insert immediately thereafter "kk."

Page 25, line 25, overstrike "kk." and insert immediately thereafter "ll."

Page 25, line 26, overstrike "ll." and insert immediately thereafter "mm."

Page 25, line 27, overstrike "mm." and insert immediately thereafter "nn."

Page 25, line 28, overstrike "nn." and insert immediately thereafter "oo."

Page 25, line 29, overstrike "oo." and insert immediately thereafter "pp."

Page 25, line 30, overstrike "pp." and insert immediately thereafter "qq."

Page 25, line 31, overstrike "qq." and insert immediately thereafter "rr."

Page 26, line 1, overstrike "rr." and insert immediately thereafter "ss."

Page 26, line 2, overstrike "ss." and insert immediately thereafter "tt."

Page 26, line 3, overstrike "tt." and insert immediately thereafter "uu."

Page 26, line 4, overstrike "uu." and insert immediately thereafter "vv."

Page 26, line 5, overstrike "vv." and insert immediately thereafter "ww."

Page 26, line 6, overstrike "ww." and insert immediately thereafter "xx."

Page 26, line 7, overstrike "xx." and insert immediately thereafter "yy."

Page 26, line 8, overstrike "yy." and insert immediately thereafter "zz."

Page 26, line 9, overstrike "zz." and insert immediately thereafter "aaa."

Page 26, line 10, overstrike "aaa." and insert immediately thereafter "bbb."

Page 26, line 11, overstrike "bbb." and insert immediately thereafter "ccc."

2  
24

Page 28, after line 19, insert:

**"SECTION 5. EMERGENCY.** This Act is declared to be an emergency measure."

Renumber accordingly

Date: 1-23-13  
Roll Call Vote #: 1

2013 HOUSE STANDING COMMITTEE  
ROLL CALL VOTES  
BILL/RESOLUTION NO. HB 1070

House Judiciary Committee

Check here for Conference Committee

Legislative Council Amendment Number \_\_\_\_\_

Action Taken:  Do Pass  Do Not Pass  Amended  Adopt Amendment  
 Rerefer to Appropriations  Reconsider

Motion Made By Rep. Delmore Seconded By Rep. Larson

Representatives	Yes	No	Representatives	Yes	No
Chairman Kim Koppelman			Rep. Lois Delmore		
Vice Chairman Lawrence Klemin			Rep. Ben Hanson		
Rep. Randy Boehning			Rep. Kathy Hogan		
Rep. Roger Brabandt					
Rep. Karen Karls					
Rep. William Kretschmar					
Rep. Diane Larson					
Rep. Andrew Maragos					
Rep. Gary Paur					
Rep. Vicky Steiner					
Rep. Nathan Toman					

Total (Yes) \_\_\_\_\_ No \_\_\_\_\_

Absent \_\_\_\_\_

Floor Assignment \_\_\_\_\_

If the vote is on an amendment, briefly indicate intent:

*Voice Vote - Carried*

Date: 1-23-13  
 Roll Call Vote #: 7

**2013 HOUSE STANDING COMMITTEE  
 ROLL CALL VOTES  
 BILL/RESOLUTION NO. H 121070**

House Judiciary Committee

Check here for Conference Committee

Legislative Council Amendment Number \_\_\_\_\_

Action Taken:  Do Pass  Do Not Pass  Amended  Adopt Amendment  
 Rerefer to Appropriations  Reconsider

Motion Made By \_\_\_\_\_ Seconded By \_\_\_\_\_

Representatives	Yes	No	Representatives	Yes	No
Chairman Kim Koppelman	/		Rep. Lois Delmore	/	
Vice Chairman Lawrence Klemin	/		Rep. Ben Hanson	/	
Rep. Randy Boehning	/		Rep. Kathy Hogan	/	
Rep. Roger Brabandt	/				
Rep. Karen Karls	/				
Rep. William Kretschmar	/				
Rep. Diane Larson	/				
Rep. Andrew Maragos					
Rep. Gary Paur					
Rep. Vicky Steiner	/				
Rep. Nathan Toman	/				

Total (Yes) 12 No 0

Absent 2

Floor Assignment Rep Larson

If the vote is on an amendment, briefly indicate intent:

REPORT OF STANDING COMMITTEE

**HB 1070: Judiciary Committee (Rep. K. Koppelman, Chairman)** recommends **AMENDMENTS AS FOLLOWS** and when so amended, recommends **DO PASS** (12 YEAS, 0 NAYS, 2 ABSENT AND NOT VOTING). HB 1070 was placed on the Sixth order on the calendar.

Page 1, line 3, after "substances" insert "; and to declare an emergency"

Page 11, line 11, after "system" insert "; or"

Page 11, line 20, after the underscored comma insert "methylenedioxybenzyl."

Page 25, line 18, after "dd." insert "Lorcaserin.

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**"SECTION 5. EMERGENCY.** This Act is declared to be an emergency  
measure."

Renumber accordingly

**2013 SENATE JUDICIARY**

**HB 1070**

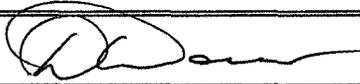
# 2013 SENATE STANDING COMMITTEE MINUTES

Senate Judiciary Committee  
Fort Lincoln Room, State Capitol

HB1070  
2/25/2013  
Job #19448

Conference Committee

Committee Clerk Signature



**Minutes:**

*Attached testimony*

## Relating to the scheduling of controlled substances

### Senator David Hogue - Chairman

Mark Hardy - Assistant Executive Director ND Board of Pharmacy - See written testimony (1)

Senator Berry asks Mr. Hardy how Tramadol got past the FDA to which he responds that the Board of Pharmacy struggles with also. He mentions that the DEA has taken preliminary steps along with the FDA to move it into a Schedule 4 Substances. He adds the evidence is outstanding that it has the narcotic effect on patients. Senator Armstrong asks him if the language regarding synthetic drugs is to make sure the garage chemist does not get ahead of the Code in two years. Mr. Hardy says we need to be as up to date as we can and stay ahead of any derivatives made in the future.

Tom Trenbeath - Attorney General's Office-Hands in testimony for the Attorney General. (2) Says they are very concerned about synthetic drugs. He says this bill in part amends the statutes so it encompasses common elements found in synthetic drugs.

Special Agent Ben Leingang - Plays an audio of a 911 call from a girl on synthetic drugs. He explains how it affects some people.

Charlene Schweitzer - Forensic Scientist - See written testimony. (3)

Senator Nelson asks Mr. Trenbeath about the relationship ND has with neighboring States drug task forces.

Dallas Carlson - BCI - Speaks of the very good relationship they have with neighboring States.

Mr. Trenbeath says if we pass this bill it will make ND on the leading edge against this crime. He explains where you buy the substance and how it is ingested. He said part of the problem is that these are purchased legal and because of that the purchaser thinks it is safe. He said they have challenged the sale of this and word will go out on the web and there will be a stampede at the shops to buy this stuff.

Senate Judiciary Committee  
HB1070  
2/25/2013  
Page 2

Opposition - none  
Neutral - none

Close the hearing on 1070

Senator Sitte moves a do pass  
Senator Grabinger seconded

Discussion

Committee discusses that this is a good bill and how to deal with mutations and not having to wait 2 years for the legislature to come in session.

Vote - 7 yes, 0 no  
Motion passes

Senator Berry will carry

Date: 2/25/13  
 Roll Call Vote #: 1

**2013 SENATE STANDING COMMITTEE  
 ROLL CALL VOTES  
 BILL/RESOLUTION NO. 1070**

Senate JUDICIARY Committee

Check here for Conference Committee

Legislative Council Amendment Number \_\_\_\_\_

Action Taken:  Do Pass  Do Not Pass  Amended  Adopt Amendment  
 Rerefer to Appropriations  Reconsider

Motion Made By S Sitte Seconded By S Grabinger

Senators	Yes	No	Senator	Yes	No
Chairman David Hogue	X		Senator Carolyn Nelson	X	
Vice Chairman Margaret Sitte	X		Senator John Grabinger	X	
Senator Stanley Lyson	X				
Senator Spencer Berry	X				
Senator Kelly Armstrong	X				

Total (Yes) 7 No 0

Absent \_\_\_\_\_

Floor Assignment S. Berry

If the vote is on an amendment, briefly indicate intent:

**REPORT OF STANDING COMMITTEE**

**HB 1070, as engrossed: Judiciary Committee (Sen. Hogue, Chairman) recommends DO PASS (7 YEAS, 0 NAYS, 0 ABSENT AND NOT VOTING). Engrossed HB 1070 was placed on the Fourteenth order on the calendar.**

**2013 TESTIMONY**

**HB 1070**

#1



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State of North Dakota

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Jack Dalrymple, Governor

Mark J. Hardy, PharmD, R.Ph.  
Assistant Executive Director  
Howard C. Anderson, Jr, R.Ph.  
Executive Director

**House Bill No 1070 – Controlled Substances Rescheduling**

House Judiciary Committee - Prairie Room

9:40 AM - Monday – January 14, 2013

Chairman Koppelman, members of the House Judiciary Committee, for the record I am Mark J. Hardy, PharmD, Assistant Executive Director of the North Dakota State Board of Pharmacy. I appreciate the opportunity to be here to speak to you today.

House Bill 1070 is the biennial bill introduced by State Board of Pharmacy to bring the Controlled Substances scheduling up-to-date with what the Food and Drug Administration [FDA] and Drug Enforcement Administration [DEA] have done over the past two years.

This bill also adds several synthetic spice cannabinoids and compounds marketed as bath salts as Class I substances. The Board of Pharmacy recently adopted an emergency rule to schedule most of these substances in North Dakota in November. The drafting of this bill, specifically the chemicals listed in schedule I was done in conjunction with the ND Crime Lab. Charlene Schweitzer, a forensic scientist with the Crime Lab is present and will be able to explain much of the chemistry and the specifics of these compounds.

This bill is very lengthy, and is as comprehensive as we feel is possible with the information we possess at this time. I want to highlight a couple items to ensure you have an understanding of the approach we have utilized in the drafting of this bill.

In section 5 on page 4 – Hallucinogenic substances. Many of the compounds that have been crossed out have been inserted in the specific section in which their chemical structure falls.

On page 7 you will notice there is language about chemical substitutions or analogs added under many of the sections that are an attempt to address all the possible chemical structure changes that may be possible. Ms. Schweitzer can explain much of these to you as well. Also under each section, we attempted to list each of the compounds, along with their accepted abbreviations in this legislation to make it easier for law enforcement and prosecuting officials to identify the substances they are working with.

Beginning on page 20 – under Anabolic steroids, there will be two additions on the next two pages that add two steroids that DEA has scheduled since our last legislative session.

On page 24 – line 14 we have proposed the drug tramadol be a Schedule IV controlled substance in the state of North Dakota. Tramadol is not currently a federally scheduled drug, but the DEA has taken preliminary steps to potentially schedule it in the future. As you may know, tramadol is currently being used as a pain medication. When tramadol is ingested, it is metabolized to a metabolite, which is a narcotic and a cousin of morphine. We have heard from many of our pharmacists about the addictive effects on patients using tramadol and from law enforcement officials about the increasing trade on the streets of tramadol selling for upwards of a \$1 per milligram. Because of the harm it is causing and the associated over dose deaths of our citizens, we certainly feel it is time to schedule this substance.

On page 28 – line 8 you will notice that we added isomers and salts of isomers and one additional chemical to the Depressants. This is also consistent with DEAs scheduling of this substance.

Lastly, I have a few proposed amendments I would like to distribute for your consideration. We would like to include an emergency measure on this bill to help speed the process of putting these changes into law as quickly as possible. Also proposed amendments would include a recent DEA scheduling of lorcaserin and two changes recommended by the ND Crime Lab.

I will be happy to answer any of your questions, and I thank you for your time.



## TRAMADOL

(Trade Names: Ultram®, Ultracet®)

February 2011  
DEA/OD/ODE

### Introduction:

Tramadol was approved for marketing as a noncontrolled analgesic in 1995 under the trade name of Ultram®. Although the company initially claimed that this substance produced only very weak narcotic effects, recent data demonstrate that opioid activity is the overriding contributor to the drug's pharmacological activity. Because of inadequate product labeling and lack of established abuse potential, many physicians felt this drug was safe to prescribe to recovering narcotic addicts and to known narcotic abusers. As a consequence, numerous reports of abuse and dependence have been received.

### Licit Uses:

Tramadol is approved for the treatment of moderate to moderately severe pain in adults. Although the Department of Health and Human Services has not recommended the scheduling of this substance in the Controlled Substances Act (CSA), a requirement necessary for DEA to place a substance under control, the Food and Drug Administration (FDA) has required the manufacturer of Ultram® to inform physicians about recent abuse data. The approved labeling has been modified on three separate occasions to include new information under the "Drug Abuse and Dependence" section. The labeling currently contains the following language:

ULTRAM may induce psychic and physical dependence of the morphine-type ( $\mu$ -opioid). Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly.

According to the IMS Health National Prescription Audit Plus™, retailers dispensed 28.2 million tramadol prescriptions in 2009. From January to September 2010, 22.2 million tramadol prescriptions were dispensed.

### Chemistry/Pharmacology:

Tramadol is a novel analgesic having both opiate agonist activity and monoamine reuptake inhibition that contribute to its analgesic efficacy. Opioid activity is due to both the parent compound and the more active O-desmethylated metabolite. Tramadol acts on the monoamine reuptake systems by inhibiting the reuptake into nerve terminals of both norepinephrine and serotonin.

Apart from analgesia, tramadol may produce a

number of symptoms including dizziness, somnolence, nausea, and constipation similar to other opioids. High doses of tramadol, often in combination monoamine oxidase (MAO) inhibitors or serotonin-selective reuptake inhibitors (SSRIs), have been associated with a serotonin syndrome consisting of convulsions, hyperthermia, muscle rigidity and pain.

Tramadol is well absorbed orally. It can be administered in 50 to 100 mg tablets as needed for pain relief every 4 to 6 hours, not to exceed 400 mg/day. Seizures have occurred in patients taking recommended doses but are more likely at high doses associated with abuse of this medication. Tolerance, dependence and addiction to tramadol have been demonstrated. Abrupt cessation from tramadol has been associated with two types of withdrawal syndromes. One is typical of opioid drugs with flu-like symptoms, restlessness and drug craving. This type of withdrawal syndrome is encountered in about 90 percent of cases of withdrawal from tramadol. Another withdrawal syndrome (encountered in about 10 percent of cases of tramadol withdrawal) is atypical of opioids and is associated with hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness and tingling in the extremities.

### Abuse and Diversion:

Tramadol is most commonly abused by narcotic addicts, chronic pain patients, and health professionals.

According to the American Association of Poison Control Centers, there were a total of 10,255 tramadol exposures in 2009. Of this total in 2009, there were 5,373 single substance exposures (4 deaths) associated with tramadol.

The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state and local forensic laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) provides information on drug seizures reported to and analyzed by DEA laboratories. Of the exhibits submitted to federal, state and local forensic laboratories in 2009, 1,291 were identified as tramadol. To date, 1,048 of the exhibits submitted to forensic laboratories in 2010 are identified as tramadol.

### Controlled Status:

Tramadol is not currently controlled under the CSA. Arkansas and Kentucky have designated tramadol as a schedule IV drug under state law. Louisiana passed legislation that identifies tramadol as a drug of abuse; demonstrating potential for abuse.

Comments and additional information are welcomed by the Office of Diversion Control, Drug and Chemical Evaluation Section. Fax 202-353-1263, Telephone 202-307-7183, or Email ODE@usdoj.gov.

BEFORE THE NORTH DAKOTA  
STATE BOARD OF PHARMACY

IN THE MATTER OF HELLERTOWN PHARMACY

Administrative No. 2011-02-17-00221-2

FINDINGS OF FACT, CONCLUSIONS OF LAW AND ORDER

On January 30, 2012, a Complaint and Statement of Charges ("Complaint") was filed with the North Dakota State Board of Pharmacy ("Board") by David A. Lindell, Special Assistant Attorney General, Counsel for the Board, and Mark J. Hardy, PharmD, Assistant Executive Director of the Board and Chairman of the Board's Investigating Committee, requesting certain administrative action against HELLERTOWN PHARMACY.

The Complaint sites as grounds for administration action, a violation of Sections 43-15-34.1, 19-02.1-15.1, and 19-03.5-02, of the North Dakota Century Code, and Section 61-12-01-02 of the North Dakota Administrative Code, as more specifically set forth in Paragraph V of the Complaint, Subsections 1, 2 and 3. The Board issued a Notice of Hearing scheduling a March 15, 2012, hearing on the Complaint. A Stipulation, Settlement Agreement and Recommendation of Discipline was stipulated and agreed to by Respondent and Howard C. Anderson, Jr., R. Ph., the Executive Director of the Board, regarding the sentence and discipline for the Respondent.

The Respondent requested that the said Stipulation not be presented to the Board at the time set forth in the Notice of Hearing so that the Owner of Hellertown Pharmacy, namely Peter J. Riccio, could attend the May 17, 2012, Board meeting. Peter Riccio informed Attorney Lindell that he would be unable to attend the Board Meeting in person, but would be available by telephone. The Board allowed Peter Riccio and his attorney, Carl Riccio, to attend via telephone, and the Board

heard from the Riccios regarding the actions of Hellertown Pharmacy in response to the Complaint and Stipulation.

NOW, THEREFORE, upon agreement of Respondent and the Executive Director of the Board, the State Board of Pharmacy makes the following:

#### FINDINGS OF FACT

1. Respondent, HELLERTOWN PHARMACY is located at 11 Main Street, Hellertown, Pennsylvania 18055. The owner of HELLERTOWN PHARMACY is Peter J. Riccio.

2. Respondent, HELLERTOWN PHARMACY does not hold an out of state permit to operate a pharmacy outside the State of North Dakota, which ships, mails and delivers in any manner or dispenses prescription drugs or legend device into North Dakota.

3. Respondent filled multiple prescriptions for patients L. F. and J.F. who are residents of North Dakota. The prescriptions for tramadol were written by physicians located in Puerto Rico, and were filled in Pennsylvania to be ultimately shipped to these patients in North Dakota without a valid patient/physician relationship existing according North Dakota Justin's Law and the tramadol prescriptions filled were not reported to the North Dakota Prescription Drug Monitoring Program.

The unauthorized prescriptions in North Dakota are as follows:

- a. Prescription No. 010770 dated May 6, 2011, written by Dr. Roberto Ruiz-Lopez, MD of 1394 San Rafael Street, San Juan, Puerto Rico 00909, to Patient J. F. for tramadol #180.
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From the foregoing FINDINGS OF FACTS and in conformity therein, the Board makes the following:

#### CONCLUSIONS OF LAW

1. Respondent agreed to be subject to the jurisdiction of the Board.
2. Respondent, HELLERTOWN PHARMACY, does not hold an out of state permit to operate a pharmacy outside the North Dakota, which ships, mails and delivers in any manner, prescriptions drug or legend devices into North Dakota.
3. Respondent, HELLERTOWN PHARMACY, has violated the following provisions of law:
  - a. Failed to obtain an out of state pharmacy permit or operating without a valid license when a license is required in violation of Section 43-15-34.1 NDCC.
  - b. Filled and dispensed prescriptions for tramadol without a valid patient/physician relationship as defined in North Dakota in violation of Justin's Law Section 19-02.1-15.1 NDCC.
  - c. Failed to report the tramadol prescriptions filled to the North Dakota Prescription Drug Monitoring Program in violation of Section 19-03.5-02 NDCC and Section 61-12-01-02 NDAC.
4. The Board of Pharmacy has the power to place on probation, reprimand or fine any pharmacy or pharmacist for the violation of the laws, rules and regulations of the practice of pharmacy in North Dakota, Section 43-15-10 NDCC.
5. The Board has the authority to direct the Pharmacy under its jurisdiction found not in compliance with the drug laws or rules of the State of North Dakota, to pay to the Board, a sum

not to exceed the reasonable, actual cost of the investigation and prosecution of the case. Section 43-15-45 NDCC.

From the foregoing FINDINGS OF FACTS and CONCLUSIONS OF LAW, the Board now makes and files herein its

ORDER

The greater weight of the evidence shows and Respondent admit in the Stipulation that it violated the provisions of law and engaged in activities and conduct that are grounds for administrative disciplinary action under the provisions of law stated in Conclusions of Law No. 3.

Because of the violations and grounds, it is hereby

ORDERED:

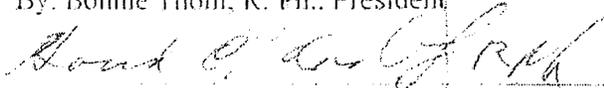
- a) Respondent shall pay to the Board a fine in the amount of \$1,750.00.

Dated this 31st day of May, 2012.

NORTH DAKOTA STATE BOARD  
OF PHARMACY



By: Bonnie Thom, R. Ph., President



Attest: Howard C. Anderson, Jr., R. Ph., Secretary

1906 East Broadway Avenue

PO Box 1354

Bismarck, ND 58502-1354

701-328-9535

1-14-13

2



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Granville  
Gayle D. Ziegler, R.Ph.  
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Mrs. Fran Gronberg  
Public Member, Bismarck

BOARD OF PHARMACY  
State of North Dakota

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Mark J. Hardy, PharmD, R.Ph.  
Assistant Executive Director  
Howard C. Anderson, Jr, R.Ph.  
Executive Director

Jack Dalrymple, Governor

### Proposed amendments to HB 1070

Page 1, Line 3 insert: and declare an emergency.

Page 11, Line 11 insert semicolon between system and by: system; by

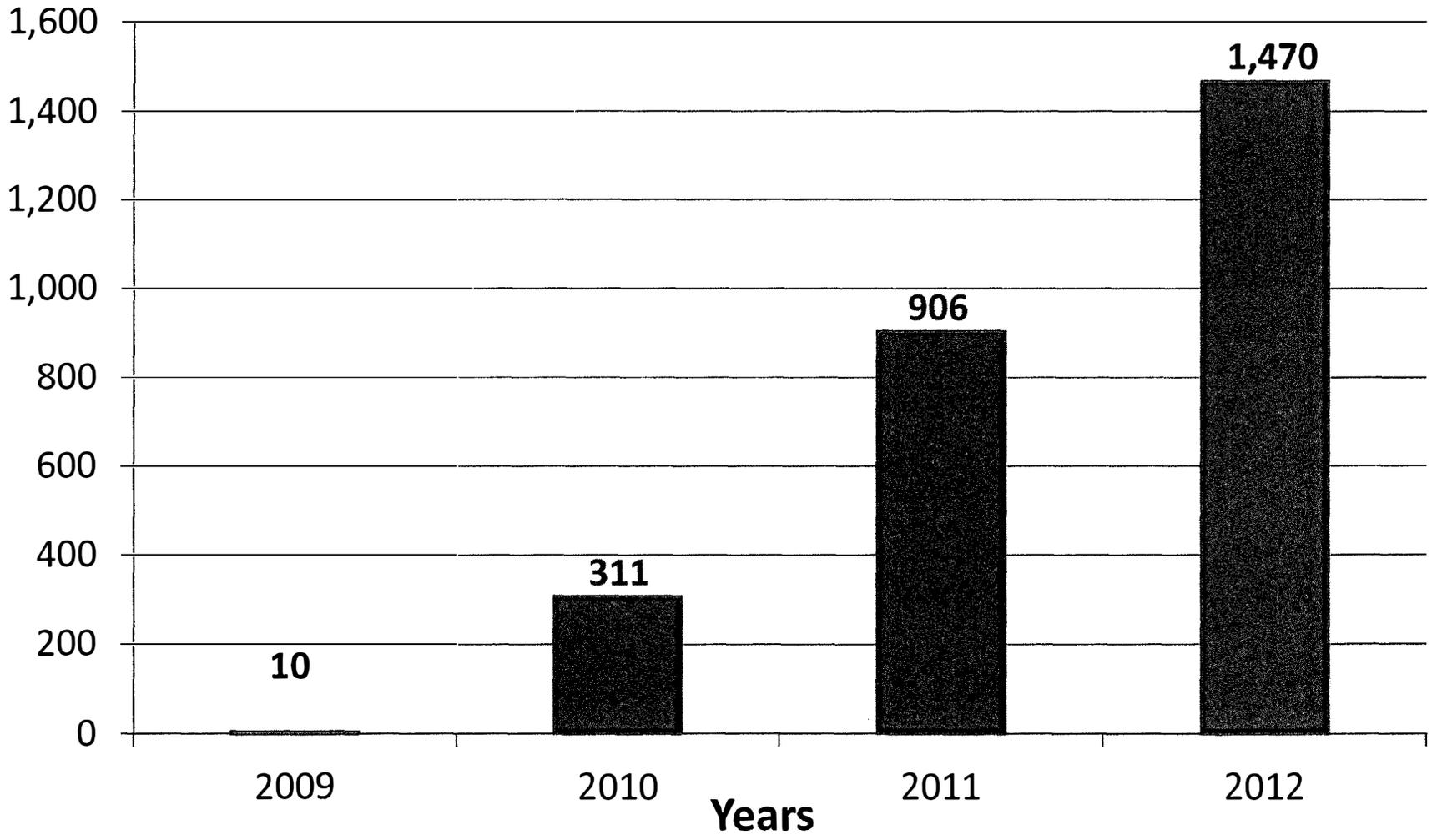
Page 11, Line 20 insert methylenedioxybenzyl: hydroxybenzyl, methylenedioxybenzyl or methoxybenzyl groups.

Page 25, Line 18 insert a new drug under Schedule IV "Depressants" and renumber accordingly:  
dd. Lorcaserin

HB1070 1-14-13  
3 Wayne Steniman

#3

# Synthetic Drug Submissions for the Period From 2009 to 2012



HB1070

1-14-13

Huf

4 - Wayne Stenzen

## Top 25 Most Used Drugs Report for Selected States

Date Range 1-2012 to 11-2012 (by Completion Date)

Description	Total	Percent
CANNABIS	4,432	47.53%
METHAMPHETAMINE	1,437	15.41%
AM-2201 (1-(5-FLUOROPENTYL)-3-(1-NAPHTHOYL)INDOLE)	247	2.65%
XLR-11 (1-(5-FLUOROPENTYL-1H-3-YL)(2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE)	243	2.61%
DIMETHYLSULFONE	218	2.34%
COCAINE	209	2.24%
AKB48 (N-(1-ADAMANTYL)-1-PENTYL-1H-INDAZOLE-3-CARBOXAMIDE)	178	1.91%
UR-144 ((1-PENTYLINDOL-3-YL)-(2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE)	156	1.67%
ACETAMINOPHEN	129	1.38%
URB754 (6-METHYL-2-[(4-METHYLPHENYL)AMINO]-1-BENZOXAZIN-4-ONE)	117	1.25%
HYDROCODONE	111	1.19%
OXYCODONE	110	1.18%
MAM-2201 (1-(5-FLUOROPENTYL)-3-(4-METHYL-1-NAPHTHOYL)INDOLE)	103	1.10%
JWH-122 (1-PENTYL-3-(4-METHYL-1-NAPHTHOYL)INDOLE)	93	1.00%
JWH-018 (1-PENTYL-3-(1-NAPHTHOYL)INDOLE)	65	0.70%
N,N-DIALLYL-5-METHOXYTRYPTAMINE (5-MEO-DALT)	64	0.69%
MORPHINE	61	0.65%
ALPRAZOLAM	60	0.64%
URB-602 (CYCLOHEXYL BIPHENYL-3-YLCARBAMATE)	59	0.63%
AMPHETAMINE	45	0.48%
CLONAZEPAM	41	0.44%
PHENYLIMIDOTHIAZOLE ISOMER UNDETERMINED	41	0.44%
CAFFEINE	39	0.42%
JWH-210 (1-PENTYL-3-(4-ETHYL-1-NAPHTHOYL)INDOLE)	39	0.42%
HYDROMORPHONE	37	0.04%
<b>Total Top 25 Drugs</b>	<b>8,334</b>	<b>89.01%</b>
<b>Total of All Drugs</b>	<b>9,325</b>	

**HB 1070**

Charlene Schweitzer  
Forensic Scientist  
January 14<sup>th</sup> 2013

4# 5 HB1070

The legal designer drug market has exploded in the last four years. The products are marketed as Incense, Potpourri, Bath Salts, and Pond Cleaner or sold on the internet as Research Chemicals and labeled "Not for Human Consumption." However, it is clearly known that they are chemicals that give psychoactive and mind altering effects. The chemicals used to create synthetic drugs are typically shipped into the United States from overseas (China, India, Korea, & Pakistan) where these chemicals are not regulated. They are easy to obtain via the internet and are typically ordered and shipped directly to the distributors that create these products or blends but also can be ordered by individual users. There are many different types of designer drugs and in the last four years the forensic community has seen many different compounds come through in waves. As new laws become enacted, the compounds are constantly changing to circumvent the laws. I will explain the current status and situation of the Cannabinoids, Stimulants, and Hallucinogens as seen by the North Dakota State Crime Laboratory.

### ***Synthetic Cannabinoids***

Synthetic Cannabinoids are synthetic chemicals that bind to the brain's cannabinoid receptors the same way as THC, the psychoactive ingredient in Marijuana. These compounds are commonly dissolved into a solvent and sprayed onto herbal smoking mixtures. The brain has two cannabinoid receptors referred to as CB1 and CB2. The CB1 receptor is associated with the central nervous system and the CB2 receptor is associated with anti-inflammatory properties. There are hundreds of these synthetic cannabinoid compounds that have been created for medicinal research to seek high affinity for the CB2 receptor for the anti-inflammatory properties without the psychoactive effects from the CB1 receptor but such separation has yet to be found. There are a large amount of synthetic cannabinoid compounds with chemically diverse structure classes so they can be quite different from one another and difficult to control as a whole. These substances have been showing up in the forensic community in waves with the first generation of compounds being the JWH compounds, which we rarely identify in current casework anymore. We are now into the 3<sup>rd</sup> generation wave of synthetic cannabinoids and new compounds keep emerging. In 2011, North Dakota passed SB2119 that placed Synthetic Cannabinoids into seven chemical classes in schedule I of the ND Century Code. This allowed the state to control hundreds of compounds via a generic group definition but the Crime Lab continues to identify new compounds that fall outside the definition of these seven classes. This bill went into effect Aug 1<sup>st</sup> 2011 and three weeks later, the Crime Lab started identifying new compounds that fell outside of the classes defined in the Century Code. It is being proposed to add an additional class (Tetramethylcyclopropanoylindoles) to the Synthetic Cannabinoids in the Century Code, which includes some of the more common compounds that the Crime Lab is recently identifying in case work. Six other additional synthetic cannabinoid compounds that are being identified in casework and don't fall into any of the classes are also being proposed to be specifically named and added to the Century Code.

## **HB 1070**

Charlene Schweitzer

Forensic Scientist

January 14<sup>th</sup> 2013

### ***Substituted Cathinones (Bath Salts)***

Substituted cathinone derivatives are based on the natural alkaloid Cathinone that is the active ingredient to the shrub Khat. These compounds are central nervous system stimulants that give users a high similar to Methamphetamine or Cocaine but can become hallucinogenic at very high doses. In 2011, North Dakota scheduled two synthetic cathinone compounds (MDPV and Mephedrone) and the DEA also emergency scheduled these two compounds along with an additional compound (Methylone) on October 21, 2011. The Crime Lab has identified eleven synthetic cathinone compounds in ND, only two of which are currently controlled, and there are numerous others that could potentially be seen. As of June 2012, twenty states have utilized some form of chemical class approach with the substituted cathinones similar to what we did with the synthetic cannabinoids. It is being proposed to do the same with these compounds and have a generic chemical class definition that would encompass these substituted cathinones and would have specific examples listed in the Century Code.

### ***Hallucinogens (Phenethylamines & Tryptamines)***

Besides the cannabinoids and cathinones there are other designer drugs such as psychedelic hallucinogens which have become increasingly popular. Two groups of hallucinogenic compounds that are encountered are the substituted Phenethylamines and substituted Tryptamines. Some of these compounds have been around for years and are already specifically listed in our law but there new derivatives or analogs that have been showing up more recently in the forensic community.

Psychedelic phenethylamines include numerous compounds that produce extreme hallucinations and mind alterations similar to LSD. On July 9<sup>th</sup> 2012, the DEA added nine of the "2C" compounds (ex: 2C-I, 2C-E, 2C-C) to the Controlled Substances Act but North Dakota has been identifying additional phenethylamine hallucinogen compounds. Two new super potent 2C derivatives (2C-I-NBOMe & 2C-C-NBOMe) have been associated with the two deaths and five other additional overdoses in the Grand Forks area this past summer. Recently I have also heard of other hospitalizations and deaths possibly associated with these substances from other states. There are hundreds of these substituted phenethylamine compounds that could be encountered and therefore, just like the cannabinoids and substituted cathinones, it is being proposed to add a generic chemical definition of this class of compounds and list specific examples under the definition. Some compounds that would fall into this class are already listed schedule I hallucinogens in the Century Code so they would be moved under this class.

Another group of hallucinogenic compounds is called the substituted tryptamines and are becoming more popular in the designer drug market. These compounds are similar to the natural compounds Psilocyn and DMT, which are already controlled substances. It is being proposed to add a chemical class definition for this class of compounds and list specific examples. Like the

**HB 1070**

Charlene Schweitzer

Forensic Scientist

January 14<sup>th</sup> 2013

Phenethylamines, some compounds may already be listed in the Century Code; therefore some would get moved under the correct class if they meet the definition.

Along with the addition of these generic class definitions, there are an additional four hallucinogenic compounds and two stimulant compounds that are being proposed that will be specifically named and listed.

In closing I must mention that one of the greatest concerns is that there is no consistency in purity or potency of these drugs, and variations in the contents of identical retail packages have been found. There is no consistency in how the drugs are mixed or in how dosages are applied and many times there are numerous compounds found together in one product. It is important for people to understand that with these synthetic drugs, quality control and quality assurance measures are not used so it is highly unlikely that people know exactly what compound or compounds they are actually ingesting. The designer drug market continues to rapidly change and compounds will continue to be identified that may or may not be included in our law. All we can do is to stay informed, aware and continue to monitor the substances being abused so we can protect our youth and citizens of North Dakota.



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BOARD OF PHARMACY  
State of North Dakota

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www.nodakpharmacy.com

Jack Dalrymple, Governor

Mark J. Hardy, PharmD, R.Ph.  
Assistant Executive Director  
Howard C. Anderson, Jr, R.Ph.  
Executive Director

### **House Bill No 1070 – Controlled Substances Rescheduling**

Senate Judiciary Committee – Fort Lincoln Room  
9:00 AM - Monday – January 25, 2013

Chairman Hogue, members of the Senate Judiciary Committee, for the record I am Mark J. Hardy, PharmD, Assistant Executive Director of the North Dakota State Board of Pharmacy. I appreciate the opportunity to be here to speak to you today.

House Bill 1070 is the biennial bill introduced by State Board of Pharmacy to bring the Controlled Substances scheduling up-to-date with what the Food and Drug Administration [FDA] and Drug Enforcement Administration [DEA] have done over the past two years.

This bill also adds several synthetic spice cannabinoids and compounds marketed as bath salts as Class I substances. The Board of Pharmacy recently adopted an emergency rule to schedule most of these substances in North Dakota in November. The drafting of this bill, specifically the chemicals listed in schedule I was done in conjunction with the ND Crime Lab. Charlene Schweitzer, a forensic scientist with the Crime Lab is present and will be able to explain much of the chemistry and the specifics of these compounds.

This bill is very lengthy, and is as comprehensive as we feel is possible with the information we possess at this time. I want to highlight a couple items to ensure you have an understanding of the approach we have utilized in the drafting of this bill.

In section 5 on page 4 – Hallucinogenic substances. Many of the compounds that have been crossed out have been inserted in the specific section in which their chemical structure falls.

On page 7 you will notice there is language about chemical substitutions or analogs added under many of the sections that are an attempt to address all the possible chemical structure changes that may be possible. Ms. Schweitzer can explain much of these to you as well. Also under each section, we attempted to list each of the compounds, along with their accepted abbreviations in this legislation to make it easier for law enforcement and prosecuting officials to identify the substances they are working with.

Beginning on page 20 – under Anabolic steroids, there will be two additions on the next two pages that add two steroids that the DEA has scheduled since our last legislative session.

On page 24 – line 14 we have proposed the drug tramadol be a Schedule IV controlled substance in the state of North Dakota. Tramadol is not currently a federally scheduled drug, but the DEA has taken preliminary steps to potentially schedule it in the future. As you may know, tramadol is currently being used as a pain medication. When tramadol is ingested, it is metabolized to a metabolite, which is a narcotic and a cousin of morphine. We have heard from many of our pharmacists about the addictive effects on patients using tramadol and from law enforcement officials about the increasing trade on the streets of tramadol selling for upwards of a \$1 per milligram. Because of the harm it is causing and the associated over dose deaths of our citizens, we certainly feel it is time to schedule this substance.

On page 28 – line 8 you will notice that we added isomers and salts of isomers and one additional chemical to the Depressants. This is also consistent with DEAs scheduling of this substance.

The House included an emergency measure on this bill to help move the process of putting these changes into law as quickly as possible. The other amendments would include a recent DEA scheduling of lorcaserin and two changes recommended by the ND Crime Lab, for the legislation to be as complete as possible, making this Bill along with House Bill 1133 Law will enact the most complete and up-to-date law on those synthetics and bath salts in the nation.

I will be happy to answer any of your questions, and I thank you for your time.



## TRAMADOL (Trade Names: Ultram®, Ultracet®)

February 2011  
DEA/OD/ODE

### Introduction:

Tramadol was approved for marketing as a noncontrolled analgesic in 1995 under the trade name of Ultram®. Although the company initially claimed that this substance produced only very weak narcotic effects, recent data demonstrate that opioid activity is the overriding contributor to the drug's pharmacological activity. Because of inadequate product labeling and lack of established abuse potential, many physicians felt this drug was safe to prescribe to recovering narcotic addicts and to known narcotic abusers. As a consequence, numerous reports of abuse and dependence have been received.

### Licit Uses:

Tramadol is approved for the treatment of moderate to moderately severe pain in adults. Although the Department of Health and Human Services has not recommended the scheduling of this substance in the Controlled Substances Act (CSA), a requirement necessary for DEA to place a substance under control, the Food and Drug Administration (FDA) has required the manufacturer of Ultram® to inform physicians about recent abuse data. The approved labeling has been modified on three separate occasions to include new information under the "Drug Abuse and Dependence" section. The labeling currently contains the following language:

ULTRAM may induce psychic and physical dependence of the morphine-type ( $\mu$ -opioid). Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly.

According to the IMS Health National Prescription Audit Plus™, retailers dispensed 28.2 million tramadol prescriptions in 2009. From January to September 2010, 22.2 million tramadol prescriptions were dispensed.

### Chemistry/Pharmacology:

Tramadol is a novel analgesic having both opiate agonist activity and monoamine reuptake inhibition that contribute to its analgesic efficacy. Opioid activity is due to both the parent compound and the more active O-desmethylated metabolite. Tramadol acts on the monoamine reuptake systems by inhibiting the reuptake into nerve terminals of both norepinephrine and serotonin.

Apart from analgesia, tramadol may produce a

number of symptoms including dizziness, somnolence, nausea, and constipation similar to other opioids. High doses of tramadol, often in combination monoamine oxidase (MAO) inhibitors or serotonin-selective reuptake inhibitors (SSRIs), have been associated with a serotonin syndrome consisting of convulsions, hyperthermia, muscle rigidity and pain.

Tramadol is well absorbed orally. It can be administered in 50 to 100 mg tablets as needed for pain relief every 4 to 6 hours, not to exceed 400 mg/day. Seizures have occurred in patients taking recommended doses but are more likely at high doses associated with abuse of this medication. Tolerance, dependence and addiction to tramadol have been demonstrated. Abrupt cessation from tramadol has been associated with two types of withdrawal syndromes. One is typical of opioid drugs with flu-like symptoms, restlessness and drug craving. This type of withdrawal syndrome is encountered in about 90 percent of cases of withdrawal from tramadol. Another withdrawal syndrome (encountered in about 10 percent of cases of tramadol withdrawal) is atypical of opioids and is associated with hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness and tingling in the extremities.

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Comments and additional information are welcomed by the Office of Diversion Control, Drug and Chemical Evaluation Section. Fax 202-353-1263, Telephone 202-307-7183, or Email ODE@usdoj.gov.

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  - b. Filled and dispensed prescriptions for tramadol without a valid patient/physician relationship as defined in North Dakota in violation of Justin's Law Section 19-02.1-15.1 NDCC.
  - c. Failed to report the tramadol prescriptions filled to the North Dakota Prescription Drug Monitoring Program in violation of Section 19-03.5-02 NDCC and Section 61-12-01-02 NDAC.
4. The Board of Pharmacy has the power to place on probation, reprimand or fine any pharmacy or pharmacist for the violation of the laws, rules and regulations of the practice of pharmacy in North Dakota, Section 43-15-10 NDCC.
5. The Board has the authority to direct the Pharmacy under its jurisdiction found not in compliance with the drug laws or rules of the State of North Dakota, to pay to the Board, a sum

not to exceed the reasonable, actual cost of the investigation and prosecution of the case. Section 43-15-45 NDCC

From the foregoing FINDINGS OF FACTS and CONCLUSIONS OF LAW, the Board now makes and files herein its

ORDER

The greater weight of the evidence shows and Respondent admit in the Stipulation that it violated the provisions of law and engaged in activities and conduct that are grounds for administrative disciplinary action under the provisions of law stated in Conclusions of Law No. 3. Because of the violations and grounds, it is hereby

ORDERED:

- a) Respondent shall pay to the Board a fine in the amount of \$1,750.00.

Dated this 31st day of May, 2012.

NORTH DAKOTA STATE BOARD  
OF PHARMACY

  
By: Bonnie Thom, R. Ph., President

  
Attest: Howard C. Anderson, Jr., R. Ph., Secretary  
1906 East Broadway Avenue  
PO Box 1354  
Bismarck, ND 58502-1354  
701-328-9535



# U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control

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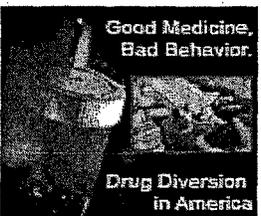
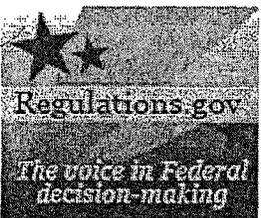
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### Rules - 2012

[Federal Register Volume 77, Number 244 (Wednesday, December 19, 2012)]

[Proposed Rules]

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[FR Doc No: 2012-30531]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-369]

Schedules of Controlled Substances: Placement of Lorcaserin Into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration (DEA) proposes placing the substance lorcaserin, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into Schedule IV of the Controlled Substances Act (CSA). This proposed action is based on a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (HHS) and on an evaluation of all other relevant data by DEA. If finalized, this action would impose the regulatory controls and criminal sanctions of Schedule IV on the manufacture, distribution, dispensing, importation, exportation, and possession of lorcaserin and products containing lorcaserin.

**DATES:** DEA will permit interested persons to file written comments on this proposal pursuant to 21 CFR 1308.43(g). Electronic comments must be submitted and written comments must be postmarked on or before January 18, 2013. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

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Interested persons, defined as those "adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811)," may file a request for hearing or waiver of participation pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45. Requests for hearing and waivers of participation must be received on or before January 18, 2013.

1121 CFR 1300.01.

**ADDRESSES:** To ensure proper handling of comments, please reference "Docket No. DEA-369" on all electronic and written correspondence. DEA encourages all comments be submitted electronically through <http://www.regulations.gov> using the electronic comment form provided on that site. An electronic copy of this document and supplemental information to this proposed rule are also available at the <http://www.regulations.gov> Web site for easy reference. Paper comments that duplicate the electronic submission are not necessary as all comments submitted to [www.regulations.gov](http://www.regulations.gov) will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments via regular or express mail, they should be sent to the Drug Enforcement Administration, Attention: DEA Federal Register Representative/OD, 8701 Morrisette Drive, Springfield, VA 22152. All requests for

hearing and waivers of participation must be sent to Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, VA 22152.

**FOR FURTHER INFORMATION CONTACT:** John W. Partridge, Executive Assistant, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152. Telephone: (202) 307-7165.

#### **SUPPLEMENTARY INFORMATION:**

##### **Posting of Public Comments**

Please note that all comments received are considered part of the public record and made available for public inspection online at <http://www.regulations.gov> and in the DEA's public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all the personal identifying information you do not want posted online or made available in the public docket 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 it to be posted online or made available in the public docket, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be posted online or made available in the public docket.

Personal identifying information and confidential business information identified and located as set forth above will be redacted and the comment, in redacted form, will be posted online and placed in the DEA's public docket file. Please note that the Freedom of Information Act applies to all comments received. If you wish to inspect the agency's public docket file in person by appointment, please see the "For Further Information Contact" paragraph, above.

##### **Requests for Hearing or Waiver of Participation in Hearing**

In accordance with the provisions of the CSA (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. 556 and 557) and 21 CFR 1308.41. Pursuant to 21 CFR 1308.44 (a) and (c), requests for a hearing and waivers of participation may be submitted only by interested persons, defined as those "adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811)." Requests for a hearing must conform to the requirements of 21 CFR 1308.44(a) and 1316.47. A request should state, with particularity, the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c), including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

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21 CFR 1300.01.

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Please note that pursuant to 21 U.S.C. 811(a), the purpose and subject matter of the hearing is restricted to "(A) find[ing] that such drug or other substance has a potential for abuse, and (B) mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed \* \* \*". Requests for hearing and waivers of participation in the hearing should be submitted to DEA using the address information provided above. DEA may grant a hearing only "for the purpose of receiving factual evidence and expert opinion regarding the issues involved in the issuance, amendment or repeal of a rule issuable" pursuant to 21 U.S.C. 811(a).

##### **Legal Authority**

DEA implements and enforces Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, often referred to as the Controlled Substances Act (CSA) and the Controlled Substances Import Export Act (CSIEA) (21 U.S.C. 801-971), as amended (hereinafter, "CSA").

Under the CSA, controlled substances are classified in one of five schedules based upon their potential for abuse, their currently accepted medical use, safety and the degree of dependence the substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances are found at 21 U.S.C. 812(c). Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, "add to such a schedule or transfer between such schedules any drug or other substance if he (A) finds that such drug or other substance has a potential for abuse, and (B) makes with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed \* \* \*". Pursuant to 28 CFR 0.100(b), the Attorney General has delegated this scheduling authority to the Administrator of DEA.

##### **Background**

Lorcaserin ((R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzepine hydrochloride hemihydrate) is a new chemical entity which has central nervous system hallucinogenic properties. Lorcaserin is a serotonin receptor agonist, at the 5HT<sub>2C</sub> and 5HT<sub>2A</sub> receptor subtypes. Lorcaserin was approved by the Food and

Drug Administration (FDA) on June 27, 2012, as an addition to a reduced-calorie diet and exercise, for chronic weight

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management and it will be marketed under the trade name BELVIQ[supreg].

#### Proposed Determination To Schedule Lorcaserin

Pursuant to the CSA, 21 U.S.C. 811(a), proceedings to add a drug or substance to those controlled under the CSA may be initiated by request of the Secretary of HHS. On June 25, 2012, HHS provided DEA with a scientific and medical evaluation document prepared by FDA entitled "Basis for the Recommendation for Control of Lorcaserin in Schedule IV of the Controlled Substances Act." Pursuant to 21 U.S.C. 811(b), (c), and (f), this document contained an eight-factor analysis of the abuse potential of lorcaserin as a new drug, along with HHS' recommendation to control lorcaserin under Schedule IV of the CSA.

In response, DEA conducted an eight-factor analysis of abuse potential of lorcaserin pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as considered by HHS and DEA. Please note that both the DEA and HHS analyses are available in whole in the "Supporting and Related Material" of the public docket for this rule at [www.regulations.gov](http://www.regulations.gov) under docket number DEA-369. Full analysis of and citations to the information referenced in the summary may be found in the supporting material.

**1. The Drug's Actual or Relative Potential for Abuse:** Lorcaserin is a new chemical substance that has not been marketed in the U.S. or in any other country. As such, there is no information available which details actual abuse of lorcaserin. However, the legislative history of the CSA offers another methodology for assessing a drug or substance's potential for abuse:

The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug 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 it has a substantial capability of creating hazards to the health of the user or to the safety of the community.<sup>131</sup>

<sup>131</sup> 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, 4601.

According to HHS, lorcaserin is an agonist at the serotonin receptor subtypes 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub>. Lorcaserin is indicated as an addition to a reduced-calorie diet and exercise, for chronic weight management. There is evidence, described below, that lorcaserin produces subjective effects in humans and in animals that are similar to those produced by zolpidem (Schedule IV) and ketamine (Schedule III)

HHS described a human abuse potential study in recreational drug abusers of psychedelic drugs and CNS depressants, in which lorcaserin and the comparator drugs zolpidem (Schedule IV) and ketamine (Schedule III) produced significant increases on positive subjective measures (visual analog scales (VAS)) for "high" and "good drug effects as well as an increase on the VAS for "hallucinations." Lorcaserin, as well as zolpidem and ketamine, significantly increased reports of "sedation" on the subjective scale of the Addiction Research Center Inventory (ARCI), compared to placebo. HHS summarized that these subjective response data suggest that lorcaserin produces subjective effects similar to those produced by zolpidem and ketamine. According to HHS, 20-60 mg of lorcaserin produced a high rate of euphoria in 6-19% of the subjects in a human abuse potential study. The incidence of euphoria following lorcaserin administration in the human abuse potential study is similar to that reported following zolpidem (Schedule IV) administration (13-16%) and lower than that following ketamine (Schedule III) administration (50%).

According to HHS, lorcaserin is not available or marketed in any country. Thus there is no evidence of lorcaserin diversion, illicit manufacturing, or deliberate ingestion. Because lorcaserin has been shown to produce euphoria in humans, it is anticipated that there will be significant use contrary to or without medical advice. Lorcaserin is not readily synthesized from available substances, and thus its diversion will be likely from the legitimate channels.

**2. Scientific Evidence of the Drug's Pharmacological Effects, If Known:** HHS stated that lorcaserin is a 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> serotonin receptor agonist. DEA further notes that it has been shown that lorcaserin through activation of 5-HT<sub>2C</sub> receptors causes inositol phosphate accumulation with an EC<sub>50</sub> of 9 nM. Lorcaserin also activated the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, with EC<sub>50</sub>s of 168 nM and 943 nM, respectively.

HHS stated that acutely, lorcaserin decreases locomotor activity in rats. Tolerance does develop to this effect, because after 21 days, lorcaserin does not affect the locomotor activity of the rats. DEA further notes that a study showed that food intake in rats was reduced after a single administration of lorcaserin. The doses administered were 3, 6, 12, and 24 mg/kg. Lorcaserin decreased the cumulative food intake at 2, 4, 6, and 22 hours. The ED<sub>50</sub> for food intake inhibition was 18 mg/kg.

According to HHS' review, a drug discrimination study conducted in 2,5-dimethoxy-4-methylamphetamine (DOM)-trained rats showed that lorcaserin (0.1-10 mg/kg) produced full generalization (= 80%) to the DOM cue in 7 of 9 rats. DOM is a Schedule I hallucinogen and a 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptor agonist. These data suggest that lorcaserin in doses 0.1 to 10 mg/kg produces discriminative stimulus responses similar to DOM, a hallucinogen.

As described by HHS in a human abuse potential study with individuals with a history of abusing drugs, lorcaserin was evaluated for its abuse potential; it was compared to ketamine (Schedule III NMDA

antagonist), zolpidem (Schedule IV GABA agonist), and a placebo. In clinical trials, lorcaserin, similar to ketamine and zolpidem, produced euphoric and hallucinogenic adverse events (AEs).

**3. The State of the Current Scientific Knowledge Regarding the Drug or Other Substance:** HHS states that lorcaserin ((R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzepine hydrochloride hemihydrate) is water-soluble. The molecular formula is C<sub>11</sub>H<sub>14</sub>ClN and its molecular weight is 241.6 g/mol, the CAS number is 616202-92-7.

According to HHS, in humans, lorcaserin is rapidly absorbed from the gastrointestinal tract after oral administration, the t<sub>max</sub> (time to reach maximum plasma concentration) is <= 2 hours and its half-life in plasma is about 11 hours. DEA further notes that after a single oral administration of 10 mg/kg lorcaserin to rats, the absorption from the gastrointestinal tract was rapid, resulting in a mean maximum plasma concentration (C<sub>max</sub>) of 0.76 [micro]g/ml at 0.25 hour. The time from oral administration to brain maximal exposure was 1 hour.

According to HHS, the major circulating metabolite of lorcaserin is lorcaserin suifamate (M1). Lorcaserin is metabolized by the liver and excreted by the kidney. M1 is considered inactive and it does not bind significantly to monoamine transporters. DEA further notes that the major metabolite in the urine is N-carbamoyl glucuronide (M5).

**4. Its History and Current Pattern of Abuse:** History and current pattern of abuse of lorcaserin is not available since it has not been marketed in any country. As stated in HHS' review, lorcaserin produced positive subjective effects in a human abuse potential study that are

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similar to those produced by zolpidem (Schedule IV) and ketamine (Schedule III). HHS states that the positive subjective effects reported from supratherapeutic doses of lorcaserin administration, are predictive of its potential for abuse.

**5. The Scope, Duration, and Significance of Abuse:** According to the HHS review, the information on lorcaserin's scope, duration and significance of abuse is not available since it has not been marketed in any country. Thus, the evaluation of the significance of abuse of lorcaserin derives from positive indicators in pre-market clinical trials which are believed to be predictive of drug abuse. Based on the AEs reported in the clinical efficacy studies and the data from a human abuse potential lorcaserin study, HHS concluded that the scope and significance of the abuse potential of lorcaserin is similar to Schedule IV substances. HHS states that marketing lorcaserin as a Schedule IV substance will decrease its abuse, as opposed to marketing it as an uncontrolled or Schedule V substance.

**6. What, if any, Risk There is to the Public Health:** According to HHS, the abuse potential of lorcaserin presents a risk to the public health. HHS states that lorcaserin produces a number of AEs that are commonly seen with other Schedule IV substances that are abused. Some of these AEs include feeling jittery, psychomotor hyperactivity, paresthesia, abnormal dreams, and state of confusion. Headache, nausea, and dizziness were the most commonly reported AEs in lorcaserin clinical studies. In a human abuse potential study, 20-60 mg lorcaserin produced a high incidence of the AE euphoria in 6-19% of the subjects. According to HHS, because lorcaserin binds to 5-HT<sub>2</sub> receptors and generalizes to 5-HT<sub>2</sub> agonists in drug discrimination studies in rats, it is expected to have a hallucinogenic profile. DEA further notes that in the human abuse potential study conducted by Shram and colleagues (2011), supratherapeutic doses of lorcaserin were associated with significantly higher peak scores on the "Detached" (40 and 60 mg), "Hallucinations" (40 mg), and "Spaced Out" (40 and 60 mg) visual analog scales.

**7. Its Psychic or Physiological Dependence Liability:** According to HHS' review, there were two clinical studies conducted to determine the ability of lorcaserin to induce physical dependence. The patients in these studies were obese and lorcaserin was administered for 4 and 12 weeks prior to drug discontinuation. Upon lorcaserin discontinuation, there were no signs of changes in mood, food interest, or body weight. Discontinuation of lorcaserin administration to animals also did not produce typical withdrawal symptoms. However, according to HHS, the ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at supratherapeutic doses is suggestive of its potential to produce psychic dependence.

**8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:** Lorcaserin is not an immediate precursor of a substance already controlled under the CSA.

**Conclusion:** Based on consideration of the scientific and medical evaluation conducted by HHS and its recommendation, and after considering its own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of lorcaserin. As such, DEA hereby proposes to schedule lorcaserin as a controlled substance under the CSA.

#### Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as Schedules I, II, III, IV, and V. The statute outlines the findings required in placing a drug or other substance in any schedule. **21 U.S.C. 812 (b).** After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b), finds that:

- (1) Lorcaserin has a low potential for abuse relative to the drugs or other substances in Schedule III. The overall abuse potential of lorcaserin is comparable to the Schedule IV substances;

(2) Lorcaserin has a currently accepted medical use in treatment in the United States. Lorcaserin was approved for marketing by FDA as an addition to a reduced-calorie diet and exercise, for chronic weight management; and

(3) Abuse of lorcaserin may lead to limited psychological dependence relative to the drugs or other substances in Schedule III. This finding is based on the ability of lorcaserin to produce positive subjective effects at supratherapeutic doses.

Based on these findings, the Administrator of DEA concludes that lorcaserin, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, warrants control in Schedule IV of the CSA (21 U.S.C. 812(b)(4)).

#### Requirements for Handling Lorcaserin

If this rule is finalized as proposed, lorcaserin would be subject to CSA regulatory controls and administrative, civil and criminal sanctions applicable to the manufacture, distribution, dispensing, importing and exporting of a Schedule IV controlled substance, including the following:

*Registration.* Any person who manufactures, distributes, dispenses, imports, exports, engages in research or conducts instructional activities with lorcaserin, or who desires to manufacture, distribute, dispense, import, export, engage in instructional activities or conduct research with lorcaserin, would need to be registered to conduct such activities pursuant to 21 U.S.C. 822 and in accordance with 21 CFR Part 1301.

*Security.* Lorcaserin would be subject to Schedules III-V security requirements and would need to be manufactured, distributed, and stored pursuant to 21 U.S.C. 823 and in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c), 1301.76, and 1301.77.

*Labeling and Packaging.* All labels and labeling for commercial containers of lorcaserin which are distributed on or after finalization of this rule would need to be in accordance with 21 CFR 1302.03-1302.07, pursuant to 21 U.S.C. 825.

*Inventory.* Every registrant required to keep records and who possesses any quantity of lorcaserin would be required to keep an inventory of all stocks of lorcaserin on hand pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11. Every registrant who desires registration in Schedule IV for lorcaserin would be required to conduct an inventory of all stocks of the substance on hand at the time of registration.

*Records.* All registrants would be required to keep records pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, 1304.21, 1304.22, and 1304.23.

*Prescriptions.* All prescriptions for lorcaserin or prescriptions for products containing lorcaserin would be required to be issued as a controlled substance pursuant to 21 U.S.C. 829 and in accordance with 21 CFR 1306, including but not limited to 21 CFR 1306.03-1306.06, 1306.08, 1306.09, and 1306.21-1306.27.

*Importation and Exportation.* All importation and exportation of lorcaserin would need to be done in

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accordance with 21 CFR Part 1312, pursuant to 21 U.S.C. 952, 953, 957, and 958.

*Criminal Liability.* Any activity with lorcaserin not authorized by, or in violation of, Subchapter I Part D and Subchapter II of the CSA occurring on or after finalization of this proposed rule would be unlawful.

#### Regulatory Analyses

##### Executive Orders 12866 and 13563

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. Such actions are exempt from review by the Office of Management and Budget pursuant to Section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

##### Executive Order 12988

This proposed regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform to eliminate ambiguity, minimize litigation, establish clear legal standards and reduce burden.

##### Executive Order 13132

This proposed rulemaking does not preempt or modify any provision of State law; nor does it impose enforcement responsibilities on any State; nor does it diminish the power of any State to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

##### Executive Order 13175

This proposed rule will not have tribal implications and will not impose substantial direct compliance costs on Indian tribal governments.

#### 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. Lorcaserin products, as recently approved by the FDA, will be used as an adjunct treatment of partial onset seizure. Handlers of lorcaserin will also handle other controlled substances used as anti-seizure agents, which are already subject to the regulatory requirements of the CSA.

**Unfunded Mandates Reform Act of 1995**

This rule will not result in the expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of \$136,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under provisions of the Unfunded Mandates Reform Act of 1995.

**Paperwork Reduction Act of 1995**

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995, 44 U.S.C. 3501- 3521.

**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, 21 CFR part 1308 is proposed to be amended as follows:

**PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES**

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

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

2. Section 1308.14 is amended by redesignating paragraphs (e) and (f) as paragraphs (f) and (g) and adding a new paragraph (e) to read as follows:

**Sec. 1308.14 Schedule IV.**

\*\*\*\*\*

(e) Lorcaserin. Any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers, and salts of such isomers, whenever the existence of such salts, isomers, and salts of isomers is possible:

(1) Lorcaserin..... 1625

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Dated: December 13, 2012.

**Michele M. Leonhart,**  
*Administrator.*

[FR Doc. 2012-30531 Filed 12-18-12; 8:45 am]

BILLING CODE 4410-09-P

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## 1-[3-(Trifluoro-methyl)-phenyl]piperazine

(Street Names: "TFMPP" or "Molly". Often found in combination with BZP: "A2", "Legal E" or "Legal X")

October 2011  
DEA/OD/ODE

### Introduction:

1-[3-(Trifluoro-methyl)-phenyl]piperazine (TFMPP) is an industrial chemical. It is often abused in combination with benzylpiperazine (BZP), a schedule I controlled substance. The Drug Enforcement Administration (DEA) temporarily controlled TFMPP in 2002 as a schedule I hallucinogen under the Controlled Substances Act (CSA) because of its abuse potential and lack of accepted medical use or safety. However, based on the scientific and medical evaluation conducted by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the Department of Health and Human Services (DHHS) did not recommend control of TFMPP. Accordingly, TFMPP was no longer controlled under the CSA after March 18, 2004. Recently, there has been an escalation in the abuse of TFMPP in the United States as evidenced by the increasing encounters of this substance by law enforcement officials in various states and the District of Columbia.

### Licit Uses:

TFMPP is used as an intermediate in chemical synthesis. It has no known medical use in the United States.

### Chemistry and Pharmacology:

TFMPP is an N-monosubstituted piperazine derivative available as either base or the hydrochloride salt. The base form is a slightly viscous yellowish liquid. The hydrochloride salt is a white solid. TFMPP base is an irritant.

Some pharmacological effects of TFMPP include rate-depressant effects, prevention of isolation-induced behavioral deficit, anxiolytic (high doses), anti-aggressive effects, locomotor inhibition, hyperthermia, respiratory depression, interference with circadian system, and hypophagia.

Experimental evidence suggests that TFMPP has some 3,4-methylenedioxymethamphetamine (MDMA)-like effects in animals. In rats, TFMPP generalizes (a maximum response of 77%) to the stimulus cue of MDMA. TFMPP also produces anxiety-like responses, alters thermoregulation, and has weak effects on the cardiovascular system. Like MDMA, TFMPP is a serotonin releasing agent.

Self-reported information indicates that TFMPP causes hallucinations in man. Some abusers describe TFMPP as a mild hallucinogen and report feeling mild, pleasant and mellow after ingesting TFMPP. In addition, some abusers stated that BZP enhances the effects of TFMPP.

### Illicit Uses:

TFMPP is being promoted as a legal alternative to MDMA at raves (all-night dance parties) as TFMPP or "Molly" and is often sold in combination with BZP as "ecstasy", or "A2", "legal E" or "legal X" in order to enhance its spectrum of effects. TFMPP may be abused alone for its hallucinogenic effects. TFMPP is generally administered orally as either powder, tablets or capsules. Other routes of administration include smoking and snorting.

### User Population:

Youth and young adults are the main abusers of TFMPP.

### Illicit Distribution:

The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state and local forensic laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) provides information on drug seizures reported to and analyzed by DEA laboratories. Federal, state and local forensic laboratories identified 202 substances as TFMPP in 2007 and 3,072 substances in 2010. In the first quarter of 2011, 394 substances were identified as TFMPP.

### Control Status:

TFMPP is currently not controlled under the CSA. TFMPP was temporarily placed into schedule I of the CSA on September 20, 2002 (67 FR 59161). On March 18, 2004, the DEA published a Final Rule (69 FR 12794) in the Federal Register reverting TFMPP to non-control status.

Georgia and Louisiana have enacted legislation to control TFMPP.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section, Fax 202-353-1263, Telephone 202-307-7183, or Email [ODE@usdoj.gov](mailto:ODE@usdoj.gov)

# Rules - 2012

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## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

21 CFR Part 1300

[Docket No. DEA-341F]

RIN 1117-AB31

### Classification of Two Steroids, Prostanazol and Methasterone, as Schedule III Anabolic Steroids Under the Controlled Substances Act

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Final rule.

**SUMMARY:** With the issuance of this Final Rule, the Administrator of the DEA classifies the following two steroids as "anabolic steroids" under the Controlled Substances Act (CSA): prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole) and methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstano-17[beta]-ol-3-one). These steroids and their salts, esters, and ethers are Schedule III controlled substances subject to the regulatory control provisions of the CSA.

**DATES:** Effective Date: August 29, 2012.

**FOR FURTHER INFORMATION CONTACT:** Alan G. Santos, Associate Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (202) 307-7165.

#### SUPPLEMENTARY INFORMATION:

##### Legal Authority

The DEA implements and enforces Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, often referred to as the Controlled Substances Act and the Controlled Substances Import and Export Act (21 U.S.C. 801-971), as amended (hereinafter, "CSA"). The implementing regulations for these statutes are found in Title 21 of the Code of Federal Regulations (CFR), parts 1300 to 1321. Under the CSA, controlled substances are classified in one of five schedules based upon their potential for abuse, their currently accepted medical use, and the degree of dependence the substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances by statute are found at 21 U.S.C. 812(c) and the current list of scheduled substances is published at 21 CFR Part 1308.

On November 29, 1990, the President signed into law the Anabolic Steroids Control Act of 1990 (Title XIX of Pub. L. 101-647), which became effective

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February 27, 1991. This law established and regulated anabolic steroids as a class of drugs under Schedule III of the CSA. As a result, a new anabolic steroid is not scheduled according to the procedures set out in 21 U.S.C. 811, but is administratively classified as an anabolic steroid through the rulemaking process if it meets the regulatory definition of an anabolic steroid in 21 CFR 1300.01.

On October 22, 2004, the President signed into law the Anabolic Steroid Control Act of 2004 (Pub. L. 108-358), which became effective on January 20, 2005. Section 2(a) of the Anabolic Steroid Control Act of 2004 amended 21 U.S.C. 802(41)(A) by replacing the existing definition of "anabolic steroid." The Anabolic Steroid Control Act of 2004 classifies a drug or hormonal substance as an anabolic steroid if the following four criteria are met: (A) The substance is chemically related to testosterone; (B) the substance is pharmacologically related to testosterone; (C) the substance is not an estrogen, progestin, or a corticosteroid; and (D) the substance is not dehydroepiandrosterone (DHEA). Any substance that meets these criteria is considered an anabolic steroid and must be listed as a Schedule III controlled substance.

##### Background

In a Notice of Proposed Rulemaking (NPRM) published on November 23, 2011 (76 FR 72355), DEA proposed classification of two steroids as Schedule III anabolic steroids under the CSA: Prostanazol and methasterone. DEA believes that prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole) and methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstano-17[beta]-ol-3-one) meet this definition of anabolic steroid.

Anabolic steroids are a class of drugs structurally related to the endogenous hormone testosterone that exert androgenic (masculinizing) as well as anabolic (body building) effects. These effects are mediated primarily through binding of the anabolic steroid to the androgen receptor in target tissues (Evans, 2004). Anabolic effects include promotion of protein synthesis in skeletal muscle and bone, while the androgenic effects are characterized by the development of male secondary sexual characteristics such as hair growth, deepening of the voice, glandular activity, thickening of the skin, and central nervous system effects (Kicman, 2008). Anabolic efficacy is characterized by positive nitrogen balance and protein metabolism, resulting in increases in protein synthesis and lean body mass (Evans, 2004). These effects often come at a cost to the healthy individual who experiences clear physical and psychological complications (Trenton and Currier, 2005; Brower, 2002; Hall et al., 2005).

In the United States, only a small number of anabolic steroids are approved for either human or veterinary use. Approved medical uses for anabolic steroids include treatment of androgen deficiency in hypogonadal males, adjunctive therapy to offset protein catabolism

associated with prolonged administration of corticosteroids, treatment of delayed puberty in boys, treatment of metastatic breast cancer in women, and treatment of anemia associated with specific diseases (e.g., anemia of chronic renal failure, Fanconi's anemia, and acquired aplastic anemia). However, with the exception of the treatment of male hypogonadism, anabolic steroids are not the first-line treatment due to the availability of other preferred treatment options. DEA is not aware of any legitimate medical use or New Drug Applications (NDA) for the two substances that DEA is proposing to classify by this NPRM as anabolic steroids under the definition set forth under 21 U.S.C. 802 (41)(A). Moreover, DEA has been unable to identify any chemical manufacturers currently using these substances as intermediates in their manufacturing processes.

Adverse health effects are associated with abuse of anabolic steroids and depend on several factors (e.g., age, sex, anabolic steroid used, the amount used, and the duration of use) (Hall and Hall, 2005; Quaglio et al., 2009). These include cardiovascular, dermatological, behavioral, hepatic, and gender specific endocrine side effects. Anabolic steroids have direct and indirect impact on the developing adolescent brain and behavior (Sato et al., 2008). Furthermore, adolescent abuse of anabolic steroids may result in stunted growth due to premature closure of the growth plates in long bones.

In adolescent boys, anabolic steroid abuse can cause precocious sexual development. In both girls and women, anabolic steroid abuse induces permanent physical changes such as deepening of the voice, increased facial and body hair growth, menstrual irregularities, and clitoral hypertrophy. In men, anabolic steroid abuse can cause testicular atrophy, decreased sperm count, and sterility. Gynecomastia (i.e., enlargement of the male breast tissue) can develop with the abuse of those anabolic steroids with estrogenic actions. In both men and women, anabolic steroid abuse can damage the liver and may result in high cholesterol levels, which may increase the risk of strokes and cardiovascular heart attacks. Furthermore, anabolic steroid abuse is purported to induce psychological effects such as aggression, increased feelings of hostility, and psychological dependence and addiction (Brower, 2002; Kanayama et al., 2008).

Upon abrupt termination of long-term anabolic steroid abuse, a withdrawal syndrome may appear including severe depression. Additionally, polysubstance abuse is routinely associated with anabolic steroid abuse, where ancillary drugs, including recreational and prescription drugs, are abused in response to unwanted side effects (Hall et al., 2005; Parkinson et al., 2005; Skarberg et al., 2009).

A review of the scientific literature finds adverse health effects including liver toxicity with renal failure reported in conjunction with methasterone abuse (Shah et al., 2008; Jasiurkowski et al., 2006; Singh et al., 2009; Nasr and Ahmad, 2008; and Krishnan et al., 2009). In March 2006, the U.S. Food and Drug Administration (FDA) issued a Warning Letter in response to adverse health effects associated with the product Superdrol (methasterone). In July 2009, FDA issued a warning regarding bodybuilding products containing steroid or steroid-like substances. In this warning, a product containing the THP ether derivative of prostanazol was named in conjunction with other products presenting safety concerns.

#### Evaluation of Statutory Factors for Classification as an Anabolic Steroid

With the issuance of this Final Rule, DEA classifies prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole) and methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstan-17[beta]-ol-3-one) as anabolic steroids under the definition set forth under 21 U.S.C. 802 (41)(A). As noted previously, a drug or hormonal substance is classified as an anabolic steroid by meeting the following four definitional requirements: (A) The substance is chemically related to testosterone; (B) the substance is pharmacologically related to testosterone; (C) the substance is not an estrogen, progestin, or corticosteroid; and (D) the substance is not DHEA.

##### (A) Chemically Related to Testosterone

To classify a substance as an anabolic steroid, a substance must be chemically related to testosterone. A structure activity relationship (SAR) evaluation for each substance compared the chemical structure of the steroid to that of testosterone. Substances with a

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structure similar to that of testosterone are predicted to possess comparable pharmacological and biological activity.

Prostanazol is also known by the following name: 17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole. DEA determined that the chemical structure of prostanazol is similar to testosterone, differing by only the attachment of a pyrazole ring at carbon 2 (C2) and carbon 3 (C3) positions of the androstane skeleton, replacing the C3-keto group and the lack of a double bond between carbon 4 (C4) and carbon 5 (C5) positions. Similar modifications to testosterone's chemical structure have been documented and, in general, they have been found to be well tolerated, displaying both anabolic and androgenic activity (Fragkaki et al., 2009; Vida, 1969). Clinton and coworkers, in their synthesis of prostanazol, described the modification as a fusion of a pyrazole ring to the androstane steroidal nucleus at C2 and C3 (Clinton et al., 1961). Further analysis finds the chemical structure of prostanazol to be very similar to the anabolic steroid stanozolol. The two structures differ only about a 17[alpha]-methyl group (alpha methyl group attached to carbon 17).

Methasterone is known by the following chemical names: 2[alpha],17[alpha]-dimethyl-5[alpha]-androstan-17[beta]-ol-3-one; 2[alpha],17[alpha]-dimethyl-17[beta]-hydroxy-5[alpha]-androstano-3-one; 17[alpha]-methyl-drostanolone; methasteron; methyl-drostanolone; 2[alpha],17[alpha]-dimethyldihydrotestosterone; and 2[alpha],17[alpha]-dimethyl-etiocolan-17[beta]-ol-3-one. DEA has determined that the chemical structure of methasterone is chemically related to testosterone. The chemical structure of methasterone differs from testosterone by the following three chemical groups: An alpha methyl group at carbon 17 (C17), an alpha methyl group at C2, and the lack of a double bond between spanning C4 and C5. Removal of the C4-C5 double bond (A-ring) and methylation at the C2 and C17 positions has been shown to increase anabolic activity (Zaffroni, 1960; Fragkaki et al., 2009). Furthermore, methyl group substitution at the C2 and C17 has been reported to impair aromatization, thus, prolonging the anabolic effect (Fragkaki et al., 2009).

##### (B) Pharmacologically Related to Testosterone

A substance must also be pharmacologically related to testosterone (i.e., produce similar biological effects) to be classified as a Schedule III anabolic steroid. The pharmacology of a steroid, as related to testosterone, can be established by performing one or more of the following androgenic and anabolic activity assays: ventral prostate assay, seminal vesicle assay, levator ani assay, and androgen receptor binding and efficacy assays. These assays are described below.

Ventral Prostate Assay, Seminal Vesicle Assay, and Levator Ani Assay: The classic scientific procedure for evaluating androgenic (masculinizing) and anabolic (muscularizing) effects of a steroid is the ventral prostate assay, seminal vesicle assay, and levator ani assay. This testing paradigm allows for the direct comparison to testosterone. Select male accessory tissues (i.e., the ventral prostate, seminal vesicles, and levator ani muscle) are testosterone sensitive, specifically requiring testosterone to grow and remain healthy. Upon the removal of the testes (i.e., castration), the primary endogenous source of testosterone is eliminated causing the atrophy of the ventral prostate, seminal vesicles, and levator ani muscle (Eisenberg et al., 1949; Nelson et al., 1940; Scow, 1952; Wainman and Shipounoff, 1941). Numerous scientific studies have demonstrated the ability of exogenous testosterone or a pharmacologically similar steroid administered to rats following castration to maintain the normal weight and size of all three testosterone sensitive organs (Biskind and

Meyer, 1941; Dorfman and Dorfman, 1963; Dorfman and Kincl, 1963; Kincl and Dorfman, 1964; Nelson et al., 1940; Scow, 1952; Wainman and Shipounoff, 1941). Thus, a steroid with testosterone-like activity will also prevent the atrophy of these three testosterone-dependent organs in castrated rats.

Castrated male rats are administered the steroid for a number of days, then the rats are euthanized and the previously described tissues are excised and weighed. Tissue weights from the three animal test groups are compared, castrated animals alone, castrated animals receiving the steroid, and healthy intact animals (control), to assess anabolic and androgenic activity. A reduction in tissue weights relative to the control group suggests a lack of androgenic and/or anabolic activity. An increase in tissue weights relative to the castrated rats receiving no steroid suggests an androgenic and/or anabolic effect.

**Androgen Receptor Binding and Efficacy Assay:** Anabolic steroids bind with the androgen receptor to exert their biological effect. Affinity for the receptor is evaluated in the receptor binding assay, while the transactivation (functional) assay provides additional information as to both affinity and ability to activate the receptor. Receptor binding and transactivation studies are valuable tools in evaluating pharmacological activity and drawing comparisons to other substances. A steroid displaying affinity for the androgen receptor and properties of being an agonist in transactivation studies is determined to be pharmacologically similar to testosterone.

Studies used to evaluate anabolic steroids are the androgen receptor binding assay and the androgen receptor transactivation assay. Both are well-established and provide significant utility in evaluating steroids for affinity to their biological target and the modulation of activity. The androgen receptor binding assay provides specific detail as to the affinity of a steroid for the androgen receptor (biological target of anabolic steroids). To assess further whether the steroid is capable of activating the androgen receptor, the androgen receptor transactivation assay evaluates the binding of a steroid to the androgen receptor and subsequent interaction with DNA. In this study, transcription of a reporter gene provides information as to a steroid's ability to modulate a biological event. This activity measurement provides information as to the potency of a steroid to bind to a receptor and either initiate or inhibit the transcription of the reporter gene. The androgen receptor binding assay and androgen receptor transactivation assay are highly valuable tools in assessing the potential activity of a steroid and comparing the activity to testosterone.

**Results of the Androgenic and Anabolic Activity Assays:** DEA reviewed the published scientific literature, and pharmacological studies were undertaken to collect additional information on prostanazol and methasterone in several different androgenic and anabolic activity assays. Findings from these studies indicate that in addition to being structurally similar to testosterone, prostanazol and methasterone have similar pharmacological activity as testosterone.

#### Prostanazol

The chemical synthesis and anabolic and androgenic effects of prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole) were published in 1961 (Clinton et al., 1961). Clinton and coworkers evaluated the anabolic activity by means of nitrogen balance and androgenic activity based on weight changes of the ventral prostate of prostanazol upon subcutaneous administration to rats with the reference

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standard testosterone propionate. The potency ratio of anabolic activity to androgenic activity for prostanazol was reported to be eight (Clinton et al., 1961). In another study, prostanazol was reported to have approximately the same relative binding affinity for human sex steroid binding protein as testosterone (Cunningham et al., 1981).

To build on these findings, a pharmacological study was conducted to evaluate the anabolic and androgenic effects of prostanazol in castrated male rats. Results were compared to testosterone by a similar protocol. Administration of prostanazol to castrated male rats by subcutaneous injection prevented the atrophy (loss in weight) of the ventral prostate, seminal vesicles, and levator ani muscle. These testosterone sensitive tissues experienced increases in weight comparable to testosterone in castrated male rats. Results from this study support that prostanazol possesses both androgenic and anabolic activity. Additional studies were conducted to further assess prostanazol's anabolic effect. In a competitive binding assay, prostanazol was found to possess affinity for the androgen receptor comparable to testosterone. In the androgen receptor transactivation assay, prostanazol displayed increased activity relative to testosterone. Effects elicited by prostanazol in this transactivation assay were consistent and comparable to those of testosterone. Taken together, data from in vitro and in vivo assays indicate the pharmacology of prostanazol to be similar to testosterone.

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<sup>11</sup>The study by Bioqual, Inc., Rockville, MD, may be found at <http://www.regulations.gov> in the electronic docket associated with this rulemaking.

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#### Methasterone

The synthesis of methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstano-17[beta]-ol-3-one) was reported in 1956 and the anabolic activity in 1959 (Ringold and Rosenkranz, 1956; Ringold et al., 1959). Methasterone was described as a potent anabolic agent exhibiting weak androgenic activity in the castrated male rat (Ringold et al., 1959). Zaffaroni and coworkers reported methasterone possessed one-fifth the androgenic activity and four times the anabolic activity of the anabolic steroid methyltestosterone, when administered orally to the experimental animal (Zaffaroni et al., 1960).

Additional pharmacological studies were undertaken to further evaluate the androgenic and anabolic effects of methasterone. Methasterone was administered subcutaneously and orally to castrated male rats. By both routes of administration, methasterone prevented the atrophy (loss in weight) of ventral prostate, seminal vesicles, and levator ani muscle. Tissue weight increases for the castrated methasterone-treated animals were comparable to the castrated rats treated with testosterone and methyltestosterone. These results were consistent with earlier findings that methasterone is anabolic and androgenic (Zaffaroni, 1960; Ringold et al., 1959). Functional assays were also undertaken to further evaluate methasterone. Methasterone displayed affinity for the androgen receptor comparable to testosterone in a competitive binding assay. In the androgen receptor transactivation assay, methasterone displayed increased activity relative to testosterone. Effects elicited by methasterone in the androgen transactivation assay were consistent and comparable to those of testosterone. Collectively, in vivo and in vitro results indicate that the pharmacology of methasterone is similar to testosterone.

#### (C) Not Estrogens, Progestins, and Corticosteroids

DEA has determined that prostanazol and methasterone are unrelated to estrogens, progestins, and corticosteroids. DEA evaluated the SAR for each of the substances. The chemical structure of each substance was compared to that of estrogens, progestins, and corticosteroids, since chemical structure can be related to its pharmacological and biological activity. DEA found that these two substances lack the necessary chemical structures to impart significant estrogenic activity (e.g., aromatic A ring) (Duax et al., 1988; Jordan et al., 1985; Williams and Stancel, 1996), progestational activity (e.g., 17[beta]-alkyl group) (Williams and Stancel, 1996), or corticosteroidal activity

(e.g., 17[beta]-ketone group or 11[beta]-hydroxyl group) (Miller et al., 2002). Furthermore, methasterone was reported to display anti-estrogenic activity in mouse assay to assess estrogen stimulated uterine growth (Dorfman et al., 1961). To assess the estrogenic, progestational, and corticosteroid activity of prostanazol and methasterone, these substances were evaluated in receptor binding and functional transactivation assays. Prostanazol and methasterone showed low binding affinity for the estrogen, progesterone, and glucocorticoid receptors. Furthermore, these steroids displayed low to no transactivation mediated by the estrogen receptors, progesterone receptors, or glucocorticoid receptors. Therefore, based on these data, prostanazol and methasterone are not estrogens, progestins, or corticosteroids and these anabolic steroids are not exempt from control on this basis.

*(D) Not Dehydroepiandrosterone*

Dehydroepiandrosterone, also known as DHEA, is exempt from control as an anabolic steroid by definition (21 U.S.C. 802(41)(A)). Prostanazol and methasterone are not dehydroepiandrosterone and therefore, are not exempt from control on this basis.

**Comments Received**

On November 23, 2011, DEA published a NPRM (76 FR 72355) to classify prostanazol and methasterone as Schedule III anabolic steroids. The proposed rule provided an opportunity for all interested persons to submit their comments on or before January 23, 2012. In response to the request, DEA received three comments.

*Comment:* One commenter disagreed that anabolic steroids, and in particular those encountered in dietary supplements, should be placed in Schedule III of the CSA. He indicated that classifying these substances as Schedule III anabolic steroids would force the public to procure other, non-regulated and unsafe substitutes from illicit sources in the future, and that DEA should employ an alternate method of regulation.

*DEA Response:* DEA disagrees with this comment. As stated in the NPRM and this Final Rule, these substances were found to be similar in structure and pharmacology to testosterone through substantive scientific evaluation and investigation. Further, the United States Food and Drug Administration has issued multiple warnings regarding dietary supplements, especially concerning contamination through novel synthetic steroids that do not qualify as dietary ingredients.

Regarding the commenter's request for alternative regulation of these substances, DEA regulates the manufacture, importation, export, distribution, and sale of controlled substances for medical, scientific, or other legitimate uses pursuant to the CSA. These substances have not been approved as safe for human consumption and, despite the commenter's unsubstantiated and factually inaccurate claims of their benefits, should neither be consumed nor should other unapproved substances ever be sought from any source, illicit or otherwise.

The additional remarks this commenter made regarding a perceived

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disparity between men and women in access to hormonal products, and other perceived problems with the regulation of substances by the government, are not germane to this rulemaking.

*Comment:* Two separate commenters agreed placement of these two substances under the CSA was appropriate as provided per the Anabolic Steroid Control Act of 2004.

*DEA Response:* DEA appreciates the support for this rulemaking. As discussed above, prostanazol and methasterone are similar in structure and pharmacology to testosterone and are not approved for human consumption. DEA believes their placement into Schedule III as anabolic steroids will provide the appropriate safeguards to limit their availability to and prevent their abuse by the public.

**Conclusion**

After evaluation of the statutory factors above and consideration of the comments to the NPRM, DEA concludes that prostanazol and methasterone meet the CSA definition of "anabolic steroid" because each substance is: (A) Chemically related to testosterone; (B) pharmacologically related to testosterone; (C) not an estrogen, progestin, or a corticosteroid; and (D) not DHEA (21 U.S.C. 802(41)). Once a substance is determined to be an anabolic steroid, DEA has no discretion regarding the placement of these substances into Schedule III of the CSA.

**Impact of Classification as Anabolic Steroids**

With the publication of this Final Rule, DEA classifies prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2-c]pyrazole) and methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstano-17[beta]-ol-3-one) as Schedule III anabolic steroids subject to the CSA. Any person who manufactures, distributes, dispenses, imports, or exports prostanazol or methasterone, or who engages in research or conducts instructional activities with respect to these two substances, will be required to obtain a Schedule III registration in accordance with the CSA and its implementing regulations.

As of the effective date of this Final Rule, the manufacture, import, export, distribution, or sale of prostanazol or methasterone, except by DEA registrants, is a violation of the CSA that may result in imprisonment and fines (see, e.g., 21 U.S.C. 841 and 960). Possession of these two steroids, unless legally obtained, is also subject to criminal penalties pursuant to 21 U.S.C. 844.

Manufacturers and importers of these two substances will be required to register with DEA and will be permitted to distribute these substances only to other DEA registrants. Only persons registered as dispensers will be allowed to dispense these substances to end users. The CSA defines a practitioner as "a physician, dentist, veterinarian, scientific investigator, pharmacy, hospital, or other person licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he practices or does research, to distribute, dispense, conduct research with respect to, administer, or use in teaching or chemical analysis, a controlled substance in the course of professional practice or research." 21 U.S.C. 802(21). At present, there are no approved medical uses for these two substances. Until a manufacturer applies to the FDA and gains approval for products containing these substances, no person may dispense them in response to a prescription.

Additionally, these two substances may only be imported for medical, scientific, or other legitimate uses (21 U.S.C. 952(b)) under an import declaration filed with DEA (21 CFR 1312.18). Importation of these substances will be illegal unless the person importing these substances is registered with DEA as an importer or researcher and files the required declaration for each shipment. Any individual who purchases either of these substances directly from foreign companies and has them shipped to the United States will be considered to be importing even if the steroids are intended for personal use. Illegal importation of these substances will be a violation of the CSA that may result in imprisonment and fines pursuant to 21 U.S.C. 960.

**Requirements for Handling Substances Defined as Anabolic Steroids**

As of the effective date of this Final Rule, prostanazol and methasterone are subject to CSA regulatory controls and the administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importation, and exportation of a Schedule III controlled substance, including the following:

**Registration.** Any person who manufactures, distributes, dispenses, imports, exports, or engages in research or conducts instructional activities with a substance defined as an anabolic steroid, or who desires to engage in such activities, will be required to be registered to conduct such activities with Schedule III controlled substances in accordance with 21 CFR Part 1301.

**Security.** Substances defined as anabolic steroids will be subject to Schedule III security requirements and will be required to be manufactured, distributed, and stored in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c), 1301.76 and 1301.77.

**Labeling and Packaging.** All labels and labeling for commercial containers of substances defined as anabolic steroids will be required to comply with the requirements of 21 CFR 1302.03-1302.07.

**Inventory.** Every registrant required to keep records and who possesses any quantity of any substance defined as an anabolic steroid will be required to keep an inventory of all stocks of the substances on hand pursuant to 21 U.S.C. 827 and 21 CFR 1304.03, 1304.04 and 1304.11. Every registrant who desires registration in Schedule III for any substance defined as an anabolic steroid will be required to conduct an inventory of all stocks of the substances on hand at the time of registration.

**Records.** All registrants will be required to keep records, as generally provided in 21 U.S.C. 827(a) and specifically pursuant to 21 CFR 1304.03, 1304.04, 1304.05, 1304.21, 1304.22, and 1304.23.

**Prescriptions.** All prescriptions for these Schedule III substances or for products containing these Schedule III substances, if approved in the future by FDA, will be required to be issued pursuant to 21 U.S.C. 829(b) and 21 CFR 1306.03-1306.06 and 1306.21-1306.27. All prescriptions for these Schedule III compounds or for products containing these Schedule III substances, if authorized for refilling, will be limited to five refills within six months of the date of issuance of the prescription. Controlled substance dispensing via the Internet will have to comply with 21 U.S.C. 829(e).

**Importation and Exportation.** All importation and exportation of any substance defined as an anabolic steroid will be required to be in compliance with 21 U.S.C. 952(b), 953(e), and 21 CFR Part 1312.

**Disposal.** Persons who possess substances that become classified as anabolic steroids and who wish to dispose of them rather than becoming registered to handle them should contact their local DEA Diversion field office for assistance in disposing of these substances legally pursuant to 21 CFR 1307.21. The DEA Diversion field office will provide the person with instructions regarding the disposal. A list of local DEA Diversion field offices may be found at <http://www.deadiversion.usdoj.gov>.

**Criminal Liability.** Any activity with any substance defined as an anabolic

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steroid not authorized by, or in violation of, the Controlled Substances Act or the Controlled Substances Import and Export Act will be unlawful.

## Regulatory Analyses

### Regulatory Flexibility Act

The Administrator hereby certifies that this rulemaking has been drafted in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612). This regulation will not have a significant economic impact on a substantial number of small entities. As of March 2010, DEA had identified approximately 75 dietary supplements that were currently or had been promoted for building muscle and increasing strength that purported to contain prostanazol or methasterone. Thirteen dietary supplements were purported to contain prostanazol and 62 dietary supplements were purported to contain methasterone. These dietary supplements are marketed and sold over the Internet.

The manufacturers and distributors of dietary supplements purported to contain prostanazol and methasterone also sell a variety of other dietary supplements. DEA has identified a substantial number of Internet distributors that sell these dietary supplements. However, these distributors also sell a variety of other nutritional products. Without information on the percentage of revenues derived from these dietary supplements, DEA is not able to determine the economic impact of the removal of these dietary supplements alone on the business of the firms. These steroids have been the focus of warning letters issued by the FDA. However, products continue to be marketed despite these warnings. DEA has not been able to identify any chemical manufacturers that are currently using these substances as intermediates in their manufacturing process(es). As of March 2010, DEA had identified 13 chemical manufacturers and distributors that sell at least one of the two steroids. Most of these companies are located in China and sell a variety of other anabolic steroids. DEA notes that, as the vast majority of entities handling these substances are Internet based, it is virtually impossible to accurately quantify the number of persons handling these substances at any given time. DEA has not identified any company based in the United States that manufactures or distributes these substances. DEA notes, upon placement into Schedule III, these substances may be used for analytical purposes. These companies are registered with DEA and are already in compliance with the CSA and DEA implementing regulations regarding the handling of Schedule III substances.

### Executive Orders 12866 and 13563

This rulemaking has been drafted in accordance with the principles of Executive Order 12866, 1(b), as reaffirmed by Executive Order 13563. This rule is not a significant regulatory action but has been reviewed by the Office of Management and Budget. As discussed above, the effect of this rule will be to remove products containing these substances from the over-the-counter marketplace. DEA has no basis for estimating the size of the market for these products. DEA notes, however, that virtually all of the substances are imported. According to U.S. International Trade Commission data, the import value of all anabolic steroids in 2009 was \$5.9 million. These two substances would be a subset of those imports. The total market for products containing these substances, therefore, is probably quite small. Moreover, DEA believes that the importation of these two substances is for illegitimate purposes.

The benefit of controlling these substances is to remove from the marketplace substances that have dangerous side effects and no legitimate medical use in treatment in the United States. As discussed in detail above, these substances can produce serious health effects in adolescents and adults. If medical uses for these substances are developed and approved, the drugs would be available as Schedule III controlled substances in response to a prescription issued by a medical professional for a legitimate medical purpose. Until that time, however, this action will bar the importation, exportation, and sale of these two substances except for legitimate research or industrial uses.

*Executive Order 12 88*

This regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform.

*Executive Order 13132*

This rulemaking does not preempt or modify any provision of State law; nor does it impose enforcement responsibilities on any State; nor does it diminish the power of any State to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

*Executive Order 131 5*

This rule will not have tribal implications and will not impose substantial direct compliance costs on Indian tribal governments.

*Paper work Reduction Act*

This rule regulates two anabolic steroids, which are neither approved for medical use in humans nor approved for administration to cattle or other non-humans. Only chemical manufacturers who may use these substances as chemical intermediates for the synthesis of other steroids would be required to register with DEA under the CSA. However, DEA has not been able to identify any chemical manufacturers that are currently using these substances as intermediates in their manufacturing processes. Thus DEA does not expect this rule to impose any additional paperwork burden on the regulated industry.

*Unfunded Mandates Reform Act of 1995*

This rule will not result in the expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of \$136,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under the provisions of the Unfunded Mandates Reform Act of 1995, 2 U.S.C. 1532.

**List of Subjects in 21 CFR Part 1300**

Chemicals, Drug traffic control.

For the reasons set out above, 21 CFR part 1300 is amended as follows:

**PART 1300--DEFINITIONS**

- 1. The authority citation for part 1300 continues to read as follows:

**Authority:** 21 U.S.C. 802, 821, 829, 871(b), 951, 958(f).

- 2. In Sec. 1300.01, the definition of Anabolic steroid under paragraph (b) is amended by:
  - A. Redesignating paragraphs (32) through (63) as (33) through (64),
  - B. Adding a new paragraph (32),
  - C. Further redesignating newly designated paragraphs (58) through (64) as (59) through (65), and
  - D. Adding new paragraph (58). The additions read as follows:

**Sec. 1300.01 Definitions relating to controlled substances.**

\*\*\*\*\*

(b) \*\*\*

*Anabolic steroid* \*\*\*

(32) Methasterone (2[alpha],17[alpha]-dimethyl-5[alpha]-androstan- 17[beta]-ol-3-one)

\*\*\*\*\*

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(58) Prostanazol (17[beta]-hydroxy-5[alpha]-androstano[3,2- c]pyrazole)

\*\*\*\*\*

Dated: July 13, 2012.

**Michele M. Leonhart,**  
*Administrator.*

Note: The following appendix will not appear in the Code of Federal Regulations.

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# Rules - 2011

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## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-354]

### Schedules of Controlled Substances: Placement of Ezogabine Into Schedule V

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Final rule.

**SUMMARY:** With the issuance of this final rule, the Administrator of the Drug Enforcement Administration (DEA) places the substance ezogabine, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into Schedule V of the Controlled Substances Act (CSA). This action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking.

**DATES:** Effective date: December 15, 2011.

**FOR FURTHER INFORMATION CONTACT:** Rhea D. Moore, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone (202) 307-7165.

#### SUPPLEMENTARY INFORMATION:

##### Legal Authority

The DEA implements and enforces Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, often referred to as the Controlled Substances Act and the Controlled Substances Import and Export Act (21 U.S.C. 801-971), as amended (hereinafter, "CSA"). The implementing regulations for these statutes are found in Title 21 of the Code of Federal Regulations (CFR), parts 1300 to 1321. Under the CSA, controlled substances are classified in one of five schedules based upon their potential for abuse, their currently accepted medical use, and the degree of dependence the substance may cause, 21 U.S.C. 812. The initial schedules of controlled substances by statute are found at 21 U.S.C. 812(c) and the current list of scheduled substances is published at 21 CFR Part 1308.

Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, "add to such a schedule or transfer between such schedules any drug or other substance if he (A) Finds that such drug or other substance has a potential for abuse, and (B) makes with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed \* \* \*

\*\* Pursuant to 28 CFR 0.100(b), the Attorney General has delegated this scheduling authority to the Administrator of DEA.

The CSA provides that 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 HHS, or (3) on the petition of any interested party, 21 U.S.C. 811(a). This action is based on a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (HHS) and on an evaluation of all other relevant data by DEA. This action imposes the regulatory controls and criminal sanctions of Schedule V on the manufacture, distribution, dispensing, importation, and exportation of ezogabine and products containing ezogabine.

Pursuant to 21 CFR 1308.44(e), the Administrator of DEA may issue her final order "[i]f all interested persons waive or are deemed to waive their opportunity for the hearing or to participate in the hearing." As no requests for a hearing were filed on this proposed scheduling action, all interested persons are deemed to have waived their opportunity for a hearing pursuant to 21 CFR 1308.44(d), and the Administrator may issue her final order without a hearing.

Ezogabine is a new drug with a novel mechanism of action for the treatment of partial onset seizures. Because ezogabine is a new drug with possible immediate medical application to a life-threatening illness not always treatable with medications currently available and because it may not be prescribed in the United States until this final rulemaking action is in effect and the subsequent requirements that result from this final action are satisfied, the Administrator hereby finds that it is in the interest of public health to forego the 30 day period prior to this final rule taking effect. This will impose no hardship on any interested party and is responsive to comments intended to facilitate the availability of ezogabine as soon as possible for that population of people suffering from seizures that may benefit from treatment with ezogabine. Therefore, in accordance with this finding of conditions of public health and of good cause to waive the 30 day period and pursuant to 21 CFR 1308.45 and 5 U.S.C. 553(d)(3), this final rule is effective upon publication.

##### Background

Ezogabine, known chemically as N-[2-amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester, is a new chemical substance with central nervous system depressant properties and is classified as a sedative-hypnotic. Pharmacological studies indicate that ezogabine primarily acts as a ligand at ion-gated channels in the brain to enhance potassium currents mediated by neuronal KCNQ (Kv7) channels. Additionally, ezogabine indirectly enhances the gamma-aminobutyric acid (GABA) mediated neurotransmission. On June 10, 2011, the Food and Drug Administration (FDA) approved a New Drug Application (NDA) for ezogabine as an adjunct treatment of partial onset seizures, to be marketed under the trade name Potiga[supreg].<sup>11</sup>

## Determination To Schedule Ezogabine

Pursuant to 21 U.S.C. 811(a), proceedings to add a drug or substance to those controlled under the CSA may be initiated by request of the Secretary of HHS. On January 12, 2011, HHS provided DEA with a scientific and medical evaluation document prepared by FDA entitled "Basis for the Recommendation for Control of Ezogabine in Schedule V of the Controlled Substances Act." Pursuant to 21 U.S.C. 811(b), this document

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contained an eight-factor analysis of the abuse potential of ezogabine as a new drug, along with HHS' recommendation to control ezogabine under Schedule V of the CSA. In response, DEA conducted an eight-factor analysis of ezogabine's abuse potential pursuant to 21 U.S.C. 811(c).

Following analysis, the Administrator of DEA published a Notice of Proposed Rulemaking entitled "Schedules of Controlled Substances: Placement of Ezogabine into Schedule V" on October 21, 2011 (76 FR 65424), which proposed placement of ezogabine into Schedule V of the CSA. The proposed rule provided an opportunity for all interested persons to request a hearing or to submit comments on or before November 21, 2011.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in the scheduling decision. Please note that both the DEA and HHS analyses are available under "Supporting and Related Material" of the public docket for this rule at [www.regulations.gov](http://www.regulations.gov) under docket number DEA-354.

**1. The Drug's Actual or Relative Potential for Abuse:** Ezogabine is a new chemical substance that has not been marketed in the U.S. As such, there is no information available which details actual abuse of ezogabine. However, the legislative history of the CSA offers another methodology for assessing a drug or substance's potential for abuse:

The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug 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 it has a substantial capability of creating hazards to the health of the user or to the safety of the community.<sup>121</sup>

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<sup>121</sup> 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, 4601.

Ezogabine acts as a ligand at ion-gated channels in the brain, similar to the Schedule V substances pregabalin and lacosamide, and, like those drugs, ezogabine is indicated for the treatment of epileptic conditions in humans. There is strong evidence, described below, that ezogabine produces behavioral effects in humans and in animals that are similar to those produced by pregabalin and lacosamide.

Phase 1 clinical studies indicate that the rate of euphoria-related adverse events (AEs) resulting from administration of ezogabine was 6-9%. This is similar to the AE rates for administration of pregabalin (10%) and lacosamide (>7%), while Phase 1/2/3 clinical studies indicated similar AE rates between ezogabine (<1%) and lacosamide (<2%). Animal studies involving administration of ezogabine to animals produced a sedative behavioral profile similar to that produced from administration of pregabalin and lacosamide, including decreased locomotion, decreased muscle tone, and an increase in ataxia. Further, in abuse potential studies conducted with sedative-hypnotic abusers, ezogabine, pregabalin, and lacosamide, when compared to placebos, are similar in their ability to produce statistically significant increases in subjective responses including "Drug Liking," "Euphoria," "Overall Drug Liking," "Good Drug Effects," and "High."

Because of the similarities between ezogabine, pregabalin, and lacosamide, it is very likely that ezogabine will have an abuse potential similar to those Schedule V substances. Currently there is a lack of evidence regarding the diversion, illicit manufacturing or deliberate misuse of ezogabine due to its commercial unavailability in any country, but since ezogabine is not readily synthesized from available substances, any diversion would be from legitimate channels. The above referenced studies, which include demonstration of the significant euphoric effects produced by ezogabine in humans, predict that there will be significant use of ezogabine contrary to or without medical advice.

**2. Scientific Evidence of the Drug's Pharmacological Effects, if Known:** Ezogabine acts to enhance potassium currents mediated by neuronal KCNQ (Kv7) channels with a secondary action through the augmentation of GABA-mediated neurotransmission without direct GABA receptor stimulation. In individuals with histories of recreational sedative-hypnotic abuse, ezogabine (300 and 600 mg orally) produced increased ratings on the primary positive subjective scales [VAS-Drug-liking, VAS-Overall Drug Liking, ARCI-MBG (Euphoria), VAS-Take Drug Again] for peak responses (Emax for the first eight hours after drug administration) that were significantly different from the placebo. This effect is similar to that produced by alprazolam (1.5 and 3.0 mg orally; Schedule IV). On secondary positive subjective scales [VAS- High, VAS-Good Effects, ARCI-Amphetamine (Activation)] for peak responses, both ezogabine and alprazolam produced significant increases compared to the placebo, while there were no differences between ezogabine and alprazolam on those measures.

In human abuse potential studies, ezogabine (300 and 600 mg), upon oral administration, increased ratings on negative and sedating subjective measures [VAS-Bad Effects, ARCI-LSD (dysphoria) and ARCI-PCAG (sedation)] compared to the placebo, but these increases were lower than those produced by 1.5 and 3.0 mg alprazolam. These data for ezogabine are similar to those produced by lacosamide. A 900 mg dose of ezogabine produced VAS-Drug Liking and VAS-Good Effects that were higher than those produced by the two lower doses of ezogabine and either dose of alprazolam. However, the changes in VAS-Bad Effects and ARCI-LSD (dysphoria) following 900 mg ezogabine were less than or similar to those produced by lower doses of ezogabine and either dose of alprazolam. The adverse events following 900 mg ezogabine are similar to those described in the NDA file for the human abuse potential study conducted with lacosamide. These included euphoria, somnolence, visual disturbances, and altered auditory perception.

In human abuse potential studies, ezogabine, similar to pregabalin and lacosamide, also produced ratings on each of the positive subjective responses that were statistically similar to those produced by Schedule IV benzodiazepines (alprazolam or diazepam). Although this appears to suggest that these drugs have an abuse potential similar to that of Schedule IV substances, the other data from human abuse potential studies, the adverse effect profile data from safety and efficacy studies, and the data from the preclinical animal behavioral studies demonstrate that ezogabine has abuse potential less than that of Schedule IV drugs but similar to that of Schedule V drugs.

**3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance:** The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester. It is an achiral molecule with a molecular formula of C<sub>16</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub> and a molecular

weight of 303.3 g/mol. Ezogabine is a non-hygroscopic white to slightly colored powder with a melting point of 140-143 [deg]C. It is soluble in 0.9% saline, methanol, chloroform, but only sparingly soluble in ethanol and 0.1N HCL.

Ezogabine in humans has a Tmax (time required for ezogabine to reach maximum plasma concentration) ranging from 1-4 hours following both

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acute and multiple dosing, and, without the involvement of cytochrome P450, undergoes an extensive and almost exclusively phase 2 metabolic biotransformation. Ezogabine is predominantly metabolized by N- glucuronidation, resulting in the formation of two distinct N-glucuronides of the unchanged parent drug and to a lesser extent by N- acetylation to form N-acetyl-retigabine, the major bioactive metabolite of ezogabine. The half-life of both ezogabine and N-acetyl-retigabine is approximately eight hours and the Cmax (maximum plasma concentration) of both components is dose proportional after both acute and multiple dosing, suggesting a lack of accumulation with repeated administration.

**4. Its History and Current Pattern of Abuse:** As stated in the summary of Factor 1, information on ezogabine's history and current pattern of abuse is unavailable as it has not been marketed in any country. As such, evaluation of abuse potential for ezogabine derives from positive indicators in clinical studies which are believed to be predictive of drug abuse and which are discussed in Factors 1 and 2 above.

**5. The Scope, Duration, and Significance of Abuse:** Because ezogabine has not yet been marketed, information on the scope, duration, and significance of abuse of ezogabine is unavailable. However, epidemiological data on pregabalin, a Schedule V drug with an abuse potential similar to that of ezogabine, is available from the Drug Abuse Warning Network (DAWN) database.

The "abuse frequency ratio," calculated as the ratio of nonmedical use related annual emergency department visits (as reported in DAWN) to the total number of annual prescriptions for pregabalin is less than that for the Schedule IV drug, alprazolam. Further, because ezogabine has abuse-related human and animal data in its NDA file similar to data generated for pregabalin, ezogabine is likely to have an abuse potential similar to pregabalin. The "abuse frequency ratios" for pregabalin range from 29 to 47, while those for alprazolam are approximately three to six times higher, ranging from 160 to 235. Thus, pregabalin was placed into Schedule V based both on abuse-related human and animal data submitted in its NDA and by epidemiological data which justified placement relative to drugs in Schedule IV. Given that ezogabine has abuse-related human and animal data in its NDA file similar to the data generated by pregabalin, it is likely that ezogabine will have an abuse potential similar to this Schedule V drug.

**6. What, if any, Risk There is to the Public Health:** The data indicates that ezogabine may present a serious safety risk to the public health, and the predicted level of risk is similar to that observed with pregabalin and lacosamide but less than that produced by Schedule IV benzodiazepines. In Phase 1 clinical safety studies, the overall adverse event profile following ezogabine administration was similar to those from pregabalin and lacosamide and includes not only euphoria, but also somnolence, and feeling or thinking abnormally. Further, the human abuse potential study showed that the majority of subjects receiving the 900 mg dose of ezogabine experienced multiple adverse events such as euphoria, somnolence, visual disturbance, amnesia, hypo-aesthesia, paranoia, fear, confusion and hallucination. Although the 900 mg dose is three times greater than the recommended therapeutic dose, individuals who abuse drugs typically do so at supra- therapeutic doses.

**7. Its Psychic or Physiological Dependence Liability:** Ezogabine may produce limited psychic or physiological dependence liability following extended administration. Since there are no studies detailing abrupt discontinuation of ezogabine, there are minimal adequate data to evaluate the ability of ezogabine to induce withdrawal symptoms that are indicative of physical dependence. Many of the adverse events reported from the discontinuation of ezogabine were also reported prior to its discontinuation, including dizziness, somnolence, and a state of confusion. By comparison, abrupt or rapid discontinuation of pregabalin in human studies resulted in patient-reported symptoms of nausea, headache or diarrhea, which are suggestive of physical dependence, while abrupt termination of lacosamide produced no signs or symptoms of withdrawal in diabetic neuropathic pain patients.

Unlike ezogabine and pregabalin, the withdrawal syndrome following discontinuation of Schedule IV substances such as alprazolam can range from mild dysphoria and insomnia to a major syndrome including abdominal pain, muscle cramps, vomiting, sweating, tremors and convulsions. These are similar in character to those associated with other sedative-hypnotics.

The study of ezogabine abuse potential in humans with histories of recreational abuse of sedative-hypnotics found that ezogabine produces euphoria (18-33%) in these individuals. Additionally, ezogabine produced euphoria (8.5%) in Phase 1 studies in healthy individuals. These euphoria-related adverse events following administration of ezogabine are suggestive of its ability to produce psychic dependence, and the adverse events appear to be less severe and occur less frequently than Schedule IV drugs (diazepam and alprazolam) and are more similar to those of Schedule V drugs, pregabalin and lacosamide.

**8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:** Ezogabine is not an immediate precursor of any controlled substance.

#### **Requests for a Hearing and Comments**

DEA received no requests for a hearing on this scheduling action. DEA received two comments on the NPRM to schedule ezogabine.

**Comment:** The first comment requested that ezogabine be placed into Schedule IV of the CSA instead of Schedule V as proposed. While the commenter stated that ezogabine may help those who have not had success with current epilepsy treatments, the commenter believed that ezogabine's new mechanism of action, including its effect on the central nervous system as an anticonvulsant and the potential side effects of the drug therein, warrant closer scrutiny and supervision under Schedule IV.

**DEA Response:** DEA disagrees. That ezogabine has an effect on the central nervous system is alone not enough to merit its inclusion into Schedule IV of the CSA, nor is the possibility that persons to whom ezogabine is prescribed would need to monitor their medications closely. Instead, as detailed in the HHS and DEA analyses and the HHS recommendation, studies indicate that the abuse potential and likely effects of ezogabine are similar to those of the Schedule V drugs pregabalin and lacosamide, and, therefore, merit ezogabine's inclusion into Schedule V of the CSA.

**Comment:** The second comment stated that because epilepsy is a serious and potentially life-threatening illness that may not be adequately treated with currently available medicines, conditions of public health necessitate an early effective date for the final rule pursuant to 21 CFR 1308.45. As such, the commenter requested an effective date for the rule concurrent with its publication in the Federal Register.

**DEA Response:** As stated under "Legal Authority," DEA agrees that this rule should become effective upon publication. Ezogabine, unlike the currently available anticonvulsant

medications, may act as an anticonvulsant through a novel mechanism of action. Because some patients with epilepsy do not achieve satisfactory seizure control from treatments currently in use, the availability of ezogabine becomes an important and potentially life-saving option for such patients. Thus, for public health reasons pursuant to 21 CFR 1308.45 and based on finding good cause pursuant to 5 U.S.C. 553(d)(3) as outlined, this final rule is effective upon publication in the Federal Register.

### **Scheduling 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, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of ezogabine. As such, DEA will schedule ezogabine as a controlled substance under the CSA.

### **Determination of Appropriate Schedule**

The CSA establishes five schedules of controlled substances known as Schedules I, II, III, IV, and V. The statute outlines the findings required to place a drug or other substance in any particular schedule. 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(5), finds that:

- (1) Ezogabine has a low potential for abuse relative to the drugs or other substances in Schedule IV. The overall abuse potential of ezogabine is comparable to the Schedule V substances such as pregabalin and lacosamide;
- (2) Ezogabine has a currently accepted medical use in treatment in the United States. Ezogabine was approved for marketing by FDA as an adjunct treatment of partial onset seizures; and
- (3) Abuse of ezogabine may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

Based on these findings, the Administrator of DEA concludes that ezogabine, including its salts, isomers and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, warrants control in Schedule V of the CSA (21 U.S.C. 812(b)(5)).

### **Requirements for Handling Ezogabine**

Upon the effective date of this final rule, ezogabine is subject to the CSA and the Controlled Substances Import and Export Act (CSIEA) regulatory controls and administrative, civil and criminal sanctions applicable to the manufacture, distribution, dispensing, importing and exporting of a Schedule V controlled substance, including the following:

*Registration.* Any person who manufactures, distributes, dispenses, imports, exports, engages in research or conducts instructional activities with ezogabine, or who desires to manufacture, distribute, dispense, import, export, engage in research or conduct instructional activities with ezogabine, must be registered to conduct such activities pursuant to 21 U.S.C. 822 and in accordance with 21 CFR Part 1301.

*Security.* Ezogabine is subject to Schedules III-V security requirements and must be manufactured, distributed, and stored pursuant to 21 U.S.C. 823 and in accordance with 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c), 1301.76, and 1301.77.

*Labeling and Packaging.* All labels and labeling for commercial containers of ezogabine which are distributed on or after the effective date of this final rule must be in accordance with 21 CFR 1302.03- 1302.07, pursuant to 21 U.S.C. 825.

*Inventory.* Every registrant required to keep records and who possesses any quantity of ezogabine must keep an inventory of all stocks of ezogabine on hand pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11. Every registrant who desires registration in Schedule V for ezogabine must conduct an inventory of all stocks of the substance on hand at the time of registration.

*Records.* All registrants must keep records pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, 1304.06, 1304.21, 1304.22, and 1304.23.

*Prescriptions.* Ezogabine or products containing ezogabine must be distributed or dispensed pursuant to 21 U.S.C. 829 and in accordance with 21 CFR 1306.03-1306.06, 1306.08, 1306.21, and 1306.23-1306.27.

*Importation and Exportation.* All importation and exportation of ezogabine must be done in accordance with 21 CFR Part 1312, pursuant to 21 U.S.C. 952, 953, 957, and 958.

*Criminal Liability.* Any activity with ezogabine not authorized by, or in violation of, Subchapter I Part D and Subchapter II of the CSA or the CSIEA occurring on or after the effective date of this final rule is unlawful.

### **Regulatory Analyses**

#### *Executive Orders 12866 and 13563*

In accordance with 21 U.S.C. 811(a), this 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 scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to Section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

#### *Executive Order 12988*

This regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform to eliminate ambiguity, minimize litigation, establish clear legal standards, and reduce burden.

#### *Executive Order 13132*

This rulemaking does not preempt or modify any provision of state law or impose enforcement responsibilities on any state or diminish the power of any state to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

*Executive Order 13175*

This rule will not have tribal implications and will not impose substantial direct compliance costs on Indian tribal governments.

*Paperwork Reduction Act of 1995*

This action does not impose a new collection of information under the Paperwork Reduction Act of 1995, 44 U.S.C. 3501-3521.

*Congressional Review Act*

This rule is not a major rule as defined by Sec. 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act). This rule will not result in an annual effect on the economy of \$100,000,000 or more, a major increase in costs or prices, or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign based companies in domestic and export markets.

**List of Subjects in 21 CFR Part 1308**

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

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For the reasons set out above, 21 CFR Part 1308 is amended 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), unless otherwise noted.

- 2. Section 1308.15 is amended by redesignating paragraphs (e)(1) and (2) as paragraphs (e)(2) and (3), and adding a new paragraph (e)(1) to read as follows:

**Sec. 1308.15 Schedule V.**

\*\*\*\*\*

(e) \*\*\*

(1) Ezogabine [N-[2-amino-4-(4-fluorobenzylamino)-phenyl]- carbamic acid ethyl ester]-2779

\*\*\*\*\*

Dated: December 8, 2011.

**Michele M. Leonhart,**  
*Administrator.*

[FR Doc. 2011-32172 Filed 12-14-11; 8:45 am]

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## Rules - 2012

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[Proposed Rules]

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[FR Doc No: 2012-4982]

### DEPARTMENT OF JUSTICE

#### Drug Enforcement Administration

#### 21 CFR Part 1308

[Docket No. DEA-345]

#### Schedules of Controlled Substances: Placement of Five Synthetic Cannabinoids Into Schedule I

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration (DEA) proposes placing five synthetic cannabinoids 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue) including their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into Schedule I of the Controlled Substances Act (CSA). This proposed action is pursuant to the CSA which requires that

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Such actions be made on the record after opportunity for a hearing through formal rulemaking.

**DATES:** DEA will permit interested persons to file written comments on this proposal pursuant to **21 CFR 1308.43(g)**. Electronic comments must be submitted and written comments must be postmarked on or before April 30, 2012. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

Interested persons, defined as those "adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (**21 U.S.C. 811**)," may file a request for hearing or waiver of participation pursuant to **21 CFR 1308.44** and in accordance with **21 CFR 1316.45**. Requests for hearing and waivers of participation must be received on or before April 2, 2012.

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11 21 CFR 1300.01.

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**ADDRESSES:** To ensure proper handling of comments, please reference "Docket No. DEA-345" on all electronic and written correspondence. DEA encourages all comments be submitted electronically through <http://www.regulations.gov> using the electronic comment form provided on that site. An electronic copy of this document and supplemental information to this proposed rule are also available at the <http://www.regulations.gov> Web site for easy reference. Paper comments that duplicate the electronic submission are not necessary as all comments submitted to [www.regulations.gov](http://www.regulations.gov) will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments via regular or express mail, they should be sent to the Drug Enforcement Administration, Attention: DEA Federal Register Representative/OD, 8701 Morrisette Drive, Springfield, VA 22152. All requests for hearing and waivers of participation must be sent to Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, VA 22152.

**FOR FURTHER INFORMATION CONTACT:** Alan G. Santos, Associate Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (202) 307-7165.

**SUPPLEMENTARY INFORMATION:**

*Posting of Public Comments:* Please note that all comments received are considered part of the public record and made available for public inspection online at <http://www.regulations.gov> and in the DEA's public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be posted online or made available in the public docket, 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 posted online or made available in the public docket 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 it to be posted online or made available in the public docket, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be posted online or made available in the public docket.

Personal identifying information and confidential business information identified and located as set forth above will be redacted, and the comment, in redacted form, will be posted online and placed in the DEA's public docket file. Please note that the Freedom of Information Act applies to all comments received. If you wish to inspect the agency's public docket file in person by appointment, please see the FOR FURTHER INFORMATION CONTACT paragraph.

**Request for Hearing or Waiver of Participation in Hearing**

In accordance with the provisions of the CSA (**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. 556 and 557) and **21 CFR 1308.41**. Pursuant to **21 CFR 1308.44(a)** and (c), requests for hearing and waivers of participation may be submitted only by interested persons, defined as those "adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811)." Requests for hearing must conform to the requirements of **21 CFR 1308.44(a)** and **1316.47**. A request should state, with particularity, the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of **21 CFR 1308.44(c)**, including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

Please note that pursuant to **21 U.S.C. 811(a)**, the purpose and subject matter of the hearing is restricted to "(A) find [ing] that such drug or other substance has a potential for abuse, and (B) mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of **section 812** of this title for the schedule in which such drug is to be placed \* \* \*" Requests for hearing and waivers of participation in the hearing should be submitted to DEA using the address information provided above.

**Legal Authority**

The DEA implements and enforces Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, often referred to as the Controlled Substances Act and the Controlled Substances Import and Export Act (**21 U.S.C. 801-971**), as amended (hereinafter, "CSA"). The implementing regulations for these statutes are found in Title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. Under the CSA, controlled substances are classified in one of five schedules based upon their potential for abuse, their currently accepted medical use, and the degree of dependence the substance may cause. **21 U.S.C. 812**. The initial schedules of controlled substances by statute are found at **21 U.S.C. 812(c)** and the current list of scheduled substances are published at **21 CFR Part 1308**.

The CSA permits these initial schedules to be modified by providing that 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 HHS, or (3) on the petition of any interested party. **21 U.S.C. 811(a)**. The Attorney General may, by rule, "add to such a schedule or transfer between such schedules any drug or other substance if he (A) finds that such drug or other substance has a potential for abuse, and (B) makes with respect to such drug or other substance the findings prescribed by subsection (b) of **section 812** of this title for the schedule in which such drug is to be placed \* \* \*"

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**Background**

November 24, 2010, DEA published a Notice of Intent ~~v2~~ to temporarily place five synthetic cannabinoids into Schedule I pursuant to the temporary scheduling provisions of the CSA: 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-

butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue). 75 FR 71635. Following this, on March 1, 2011, the Administrator published a Final Order in the Federal Register amending **21 CFR 1308.11(g)** to temporarily place the five synthetic cannabinoids into Schedule I of the CSA pursuant to the temporary scheduling provisions of **21 U.S.C. 811(h)**. 76 FR 11075. This Final Order, which became effective on the date of publication, was based on findings by the Administrator that the temporary scheduling of the five synthetic cannabinoids was necessary to avoid an imminent hazard to the public safety. The CSA (21 U.S.C. 811(h)(2)) requires that the temporary scheduling of a substance expire at the end of one year from the date of issuance of the order. However, if proceedings to schedule a substance pursuant to 21 U.S.C. 811(a) are pending, the temporary scheduling of a substance may be extended for up to six months. Under this provision, the temporary scheduling of the cannabinoids, which would expire on February 29, 2012, may be extended to August 29, 2012. This extension is being ordered by the Administrator in a separate action.

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\2\ This Notice of Intent was corrected on January 13, 2011. 76 FR 2287.

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As described in the March 1, 2011 Final Order, a "cannabinoid" is a class of chemical compounds in the marijuana \3\ plant that are structurally related. The cannabinoid [Delta]9-tetrahydrocannabinol (THC) is the primary psychoactive constituent of marijuana. "Synthetic cannabinoids" are a large family of chemically unrelated structures functionally (biologically) similar to THC, the active principal of marijuana.

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\3\ Note that "marihuana" is the spelling originally used in the Controlled Substances Act (CSA). This document uses the spelling that is more common in current usage, "marijuana."

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The emergence of these five synthetic cannabinoids represents a recent phenomenon in the U.S. designer drug market. Numerous products, marketed under the guise being "herbal incense," with trade names such as "Spice" and "K2" have conclusively been found to contain these five substances. These products are manufactured by spiking plant material with the synthetic cannabinoids and then distributed in a way that poses dangerous consequences to the consumer. Marketed as "legal" alternatives to marijuana, these products are being abused for their psychoactive properties and are packaged without information as to their health and safety risks.

### **Proposed Determination To Schedule Five Synthetic Cannabinoids**

This NPRM proposes the permanent scheduling of JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol pursuant to **21 U.S.C. 811(a)(1)**. On June 21, 2011, DEA requested a scientific and medical evaluation and scheduling recommendation from the Assistant Secretary of HHS for each of the five synthetic cannabinoids pursuant to 21 U.S.C. 811(b). Upon receipt and evaluation of the scientific and medical evaluation and scheduling recommendations from the Assistant Secretary, \4\ DEA concluded its analysis of all other relevant data for the proposal to place JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol into Schedule I of the CSA.

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\4\ DEA received separate Evaluations and Recommendation documents from HHS with respect to each of the five synthetic cannabinoids. HHS recommended Schedule I placement for each of these five substances on the following dates: 1-pentyl-3-(1-naphthoyl)indole (JWH-018) (January 5, 2012); 1-pentyl-3-(1-naphthoyl)indole (JWH-073) and 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200) (February 6, 2012), 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (CP-47,497) and 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol) (February 13, 2012).

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Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in the scheduling decision. Please note that both the DEA and HHS analyses are available under "Supporting and Related Material" of the public docket for this proposed rule at [www.regulations.gov](http://www.regulations.gov) under docket number DEA-345.

*1. The Drug's Actual or Relative Potential for Abuse:* The abuse potential of the five synthetic cannabinoids under evaluation is associated with their ability to evoke cannabinoid-like subjective effects similar to those evoked by the Schedule I cannabinoid delta-9- tetrahydrocannabinol (THC).

The legislative history of the CSA provides four factors to consider in determining whether a particular drug or substance has potential for abuse: \5\

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15\ 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, 4601.

- i. There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or
- ii. There is significant diversion of the drug or substance from legitimate drug channels; or
- iii. 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; or
- iv. The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug or other substance will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversion from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

With respect to the first factor, a number of case reports and case series (article grouping several case reports) have shown that individuals are taking these substances and products containing these substances in amount sufficient to induce toxic effects similar to those induced by marijuana such as anxiety, tachycardia and hallucinations. Severe toxic effects including seizures, tachyarrhythmias, extreme anxiety leading to suicide and the precipitation of psychotic episodes have also been reported following abuse of these substances or products containing these substances.

In considering evidence of significant diversion of the drug or substance from legitimate drug channels under the second factor, it must be noted that as of March 1, 2011, these synthetic cannabinoids have been temporarily controlled as Schedule I substances and thus have not been legally available unless for research purposes. The National Forensic Laboratory Information System (NFLIS) details over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 states. The System to Retrieve Information from Drug Evidence (STRIDE) also details

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reports from federal forensic laboratories identifying JWH-018, JWH-073, and JWH-200 in drug related exhibits for a period from January 2009 to December 2011.

For the third factor, there is no currently accepted medical use for any of the five synthetic cannabinoids, and, outside of an extremely limited research setting, no medical practitioner is currently licensed by law to administer them. Thus, with no accepted medical use or administering practitioners, any individuals currently taking using products containing JWH-018, JWH-073, JWH-200, CP-47,497 or cannabicyclohexanol are doing so on their own initiative without medical advice from a practitioner licensed to administer those substances.

Related to the fourth factor, HHS states that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol are cannabinoids with a potential for abuse similar to the Schedule I substances marijuana and THC. These synthetic cannabinoids appear to be marketed solely for abuse of their marijuana-like activity and because, prior to the March 1, 2011 Final Order, they were not controlled under the CSA. As such, commerce involving these synthetic cannabinoids can only be for the purposes of abuse and escaping the regulatory and criminal penalties of the CSA that pertain to marijuana.

JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol have agonist properties at the CB1 receptor. The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects of THC and related cannabinoids.

Drug discrimination is a method in which laboratory animals indicate whether a test drug produces physical or psychic perceptions similar to those produced by a known drug of abuse. Drug discrimination studies in rats suggest that JWH-018, JWH-200, JWH-073, CP-47,497, and cannabicyclohexanol have similar subjective effects as THC, while numerous anecdotal self-reports, as well as case reports and case series substantiate that these substances and their associated products are abused by humans for their hallucinogenic effects. An indication of the extent of such abuse may be found in the results of the 2011 Monitoring the Future survey of high schools students, where 1 in 9 high school seniors (11.4%) reported having used "synthetic marijuana" (products often containing synthetic cannabinoids) in the past year. These statistics make it one of the most frequently mentioned among high school seniors, second only to marijuana. Additionally, while products containing synthetic cannabinoids appear to produce subjective effects similar to marijuana, they are dissimilar to other licit and illicit drugs.

As evidence of abuse on the national scale, State public health and poison centers have issued warnings in response to adverse health effects associated with abuse of herbal incense products containing these synthetic cannabinoids. These adverse effects included tachycardia, elevated blood pressure, unconsciousness, tremors, seizures, vomiting, hallucinations, agitation, anxiety, pallor, numbness and tingling. This is in addition to the numerous public health and poison centers which have similarly issued warnings regarding the abuse of these synthetic cannabinoids and their associated products, and the ban on the use of these synthetic cannabinoids by military personnel issued in response to reported instances of abuse by active personnel.

*2. Scientific Evidence of the Drug's Pharmacological Effects, If Known:* In their recommendations for the placement of the five synthetic cannabinoids, HHS states that in vitro and preclinical studies suggest that the pharmacological effects of JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol are similar to those of THC.

The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects of THC and related cannabinoids. JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol have agonist properties at the CB1 receptor.

Animal studies also provided evidence of cannabinoid-like pharmacological effects of these synthetic cannabinoids. JWH-018, JWH-200, CP-47,497 and cannabicyclohexanol were shown to be active in all four parameters of the mouse tetrad, a well-established paradigm for evaluating substances for cannabimimetic properties, while JWH-073 was only tested, and shown to be active, in three of the four parameters of the tetrad test. JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol substitute fully for the discriminative stimulus effects of THC in laboratory animals, suggesting that they are likely to have similar subjective effects as THC, the main active ingredient of marijuana.

*3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* The appearance of these substances in the designer drug market can be traced to the initial forensic laboratory confirmation in mid-December 2008. A commercial laboratory in Frankfurt, Germany announced the identification of JWH-018 in samples of herbal incense and others were identified shortly after this initial determination.

These five cannabinoid substances have been termed 'synthetic' or 'non-classical' because they are agonists at the CB1 receptor but are structurally distinct from naturally occurring cannabinoids.

HHS has confirmed to DEA in a letter dated November 22, 2010, that there are no Investigational New Drug applications (INDs) or New Drug Applications (NDAs) for these synthetic cannabinoids. DEA is also not aware of any accepted medical use for these five synthetic cannabinoids.

*4. Its History and Current Pattern of Abuse:* Synthetic cannabinoids have been developed over the last 30 years to investigate their cannabimimetic properties and as research tools to investigate the cannabinoid systems (Huffman et al., 1994; Wiley et al., 1998). Trafficking of synthetic cannabinoids was first reported in the United States in a December 2008 encounter, where a shipment of 'Spice' was seized and analyzed by U.S. Customs and Border Patrol in Dayton, Ohio. Around the same time, in December 2008, JWH-018 and cannabicyclohexanol were identified by German forensic laboratories (EMCDDA, 2009).

JWH-018, JWH-073, JWH-200, CP-47,497, and Cannabicyclohexanol have been found alone and found laced on products that are marketed as herbal incense. The abuse of these substances and their associated products for their psychoactive effects has been widely reported and their popularity has spread rapidly since December 2008. The NFLIS has detailed over 5,450 reports from state and local forensic laboratories identifying JWH-018, JWH-073, JWH-200, CP-47,497 and/or cannabicyclohexanol in drug related exhibits for a period from January 2009 to December 2011 from 39 states. Prior to being temporarily placed in Schedule I on March 1, 2011, these products were promoted as legal alternatives to marijuana, were widely available over the Internet, and were found to be sold in gas stations, convenience stores, tobacco and head shops to all populations.

As of January 13, 2012, forty-eight states in the U.S. as well as numerous local jurisdictions and countries have controlled at least one of these five synthetic cannabinoids.

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*5. The Scope, Duration, and Significance of Abuse:* HHS states that the current scope and duration of use of the synthetic cannabinoids is likely underestimated because of the lack of widely available toxicological methods to identify its use using routine analyses (Peters and Martinez-Ramirez 2010). Additionally, since these substances were never intended for human consumption, minimal information exists as to the health implications resulting from exposure to these substances (Griffiths et al., 2010; Vardakou et al., 2010). As forensic procedures and toxicology screens are being developed, the amount of information concerning these substances and the associated products is increasing.

The abuse of synthetic cannabinoids has been associated with both acute and long-term public health and safety concerns. In the past year, increased exposure incidents have been documented by poison control centers in the

United States. As of December 31, 2011, the American Association of Poison Centers (AAPCC) has reported receiving 9,992 calls corresponding to products purportedly laced with synthetic cannabinoids. The calls represented exposed individuals from all 50 states and the District of Columbia, as well as a few calls regarding exposed individuals in Puerto Rico, U.S. Territories, foreign countries, and a category identified as "overseas/US military/ diplomatic." Several of these exposures were confirmed to involve JWH- 018 (141), and JWH-073 (12).

The increased abuse of these synthetic cannabinoids in the United States is supported by an increasing number of encounters by law enforcement. Over the past year in the United States there has been a significant increase in availability, trafficking and abuse of these substances as evident from the increasing number of encounters reported by forensic laboratories (NFLIS and STRIDE data). Product manufacturing and synthesis laboratories have been discovered, and laboratories have been found manufacturing products by lacing plant material with synthetic cannabinoids.

*6. What, if any, Risk There is to the Public Health:* Law enforcement, military, and public health officials have reported exposure incidents that demonstrate the dangers associated with these substances to both the individual abusers and other affected individuals. Two suicides, one also involving a murder, have been linked to the abuse of synthetic cannabinoids (law enforcement communication to DEA). Warnings regarding the dangers of synthetic cannabinoid abuse and associated products have been issued by numerous state public health departments and poison centers and private organizations. Detailed product analyses describe variations in the amount and type of synthetic cannabinoid laced on the plant material; this is true even within samplings of the same product.

Because they share pharmacological similarities with the Schedule I substance THC, the synthetic cannabinoids JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol pose substantial risks to the abuser. Numerous emergency department admissions have been connected to these substances, while law enforcement communications to DEA indicate multiple violent episodes linked to smoking these synthetic cannabinoids. Health warnings issued by numerous state public health departments and poison centers have described adverse health effects associated with smoking (inhaling) these products, including agitation, vomiting, tachycardia, elevated blood pressure, seizures, paranoia, hallucinations and non-responsiveness, and fatality.

Case reports describe presentations to emergency departments of individuals exposed to synthetic cannabinoids with symptoms that include anxiety and panic attacks, tremors, generalized convulsions, psychosis, heart palpitations and elevated pulse, severe gastrointestinal distress, tremors, blurred peripheral vision, nausea, and persistent vomiting with sweating. Such abuse also includes instances of persons suspected of driving under the influence of these synthetic cannabinoids, including one incident where an automobile was driven through a residence. In that case the driver claimed to have no memory of the event while a toxicology analysis confirmed that the driver had smoked a product containing JWH-018, but not any other drugs.

*7. Its Psychic or Physiological Dependence Liability:* HHS states that the pharmacological profile of JWH-018, JWH-200, JWH-073, CP- 47,497 and cannabicyclohexanol strongly suggests that they possess physiological and psychological dependence liability similar to that of the Schedule I controlled substances marijuana and THC. While no laboratory controlled clinical studies of the psychic or physical dependence potential of these five synthetic cannabinoids are currently available, their pharmacological profile indicates that the substances will have high psychic and physiologic dependence capacity.

Case reports have shown that herbal products containing synthetic cannabinoids could produce physical dependence and a withdrawal syndrome. The HHS analysis discusses one case report in which the authors concluded that the patient satisfied criteria for a diagnosis of DSM-IV and ICD-10 dependency syndrome on JWH-018. Some reported withdrawal symptoms included elevated blood pressure, restlessness, drug craving, nightmares, sweating, nausea, tremor and headache.

Because these substances act through the same molecular target as THC, the main active ingredient of marijuana, it can be reasonably expected that their physical dependence liability will be similar. Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence.

*8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:* JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol are not considered immediate precursors of any controlled substance of the CSA as defined by **Title 21, U.S.C. 802(23)**.

*Conclusion:* Based on consideration of the scientific and medical evaluations and accompanying recommendations of HHS, and based on DEA's consideration of its own eight-factor analyses, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol. As such, DEA hereby proposes to schedule JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol as controlled substances under the CSA.

**Proposed Determination of Appropriate Schedule**

The CSA establishes five schedules of controlled substances known as Schedules I, II, III, IV, and V. The statute outlines the findings required to place a drug or other substance in any particular schedule. **21 U.S.C. 812(b)**. After consideration of the analysis and recommendations of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(1), finds that:

(1) 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-

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hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue) have a high potential for abuse;

(2) 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue) have no currently accepted medical use in treatment in the United States; and

(3) there is a lack of accepted safety for use of 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue) under medical supervision.

Based on these findings, the Administrator of DEA concludes that 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol, CP-47,497 C8 homologue), including their salts, isomers and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, warrant control in Schedule I of the CSA (**21 U.S.C. 812(b)(1)**).

**Requirements for Handling Five Synthetic Cannabinoids**

If this rule is finalized as proposed, JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol would be permanently, as they are currently temporarily, subject to the CSA and the Controlled Substances Import and Export Act (CSIEA) regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, and exporting of a Schedule I controlled substance, including the following:

**Registration.** Any person who manufactures, distributes, dispenses, imports, exports, engages in research or conducts instructional activities with JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanols, or who desires to manufacture, distribute, dispense, import, export, engage in research or conduct instructional activities with any of the five synthetic cannabinoids, would need to be registered to conduct such activities pursuant to **21 U.S.C. 822 and 958** and in accordance with **21 CFR part 1301**.

**Security.** JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol would be subject to Schedule I security requirements and would need to be manufactured, distributed, and stored pursuant to **21 U.S.C. 823** and in accordance with **21 CFR 1301.71, 1301.72(a), (c) and (d), 1301.73, 1301.74, 1301.75(a) and (c), 1301.76**.

**Labeling and Packaging.** All labels and labeling for commercial containers of JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol which are distributed on or after the effective date of the finalization of this rule would need to be in accordance with **21 CFR 1302.03-1302.07**, pursuant to **21 U.S.C. 825**.

**Quotas.** Quotas for JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol will be established based on registrations granted and quota applications received pursuant to **part 1303** of Title 21 of the Code of Federal Regulations.

**Inventory.** Every registrant required to keep records and who possesses any quantity of JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol would be required to keep an inventory of all stocks of any of the five synthetic cannabinoids on hand pursuant to **21 U.S.C. 827** and in accordance with **21 CFR 1304.03, 1304.04, and 1304.11**. Every registrant who desires registration in Schedule I for any of the five synthetic cannabinoids would be required to conduct an inventory of all stocks of the substance on hand at the time of registration.

**Records.** All registrants would be required to keep records pursuant to 21 U.S.C. 827 and in accordance with 21 CFR 1304.03, 1304.04, **1304.21, 1304.22, and 1304.23**.

*Reports.* All registrants required to submit reports pursuant to 21 U.S.C. 827 and in accordance with **21 CFR 1304.33** would be required to do so regarding JWH-018, JWH-200, JWH-073, CP-47,497 and cannabicyclohexanol.

*Order Forms.* All registrants involved in the distribution of JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol pursuant to **21 U.S.C. 828** would be required to comply with the order form requirements of **21 CFR 1305**.

*Importation and Exportation.* All importation and exportation of JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol would need to be done in accordance with **21 CFR Part 1312**, pursuant to **21 U.S.C. 952, 953, 957, and 958**.

*Criminal Liability.* Any activity with JWH-018, JWH-200, JWH-073, CP-47,497 or cannabicyclohexanol not authorized by, or in violation of, Subchapter I Part D and Subchapter II of the CSA or the CSIEA occurring on or after effective date of the finalization of this proposed rule would be unlawful.

## Regulatory Analyses

### *Executive Orders 12866 and 13563*

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 scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to Section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

### *Executive Order 12988*

This proposed regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform to eliminate ambiguity, minimize litigation, establish clear legal standards, and reduce burden.

### *Executive Order 13132*

This proposed rulemaking does not preempt or modify any provision of State law; nor does it impose enforcement responsibilities on any State; nor does it diminish the power of any State to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

### *Executive Order 13175*

This proposed rule will not have tribal implications and will not impose substantial direct compliance costs on Indian tribal governments.

### *Paperwork Reduction Act of 1995*

This action does not impose a new collection of information under the Paperwork Reduction Act of 1995, 44 U.S.C. 3501-3521.

## List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control,

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Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR Part 1308 is proposed to be amended 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)**, unless otherwise noted.

2. **Section 1308.11** is amended by redesignating paragraphs (d)(18) through (35) as paragraphs (d)(19) through (36) and adding a new paragraph (d)(18) to read as follows:

**Section 1308.11 Schedule I.**

\*\*\*

(d) \* \* \*

(18) Cannabimimetic agents

- (i) 1-Butyl-3-(1-naphthoyl)indole (Other names: JWH-073).....7173
- (ii) 5-(1,1-Dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (Other names: CP-47,497).....7297
- (iii) 5-(1,1-Dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol  
(Other names: Cannabicyclohexanol and CP-47,497 C8 homologue).....7298
- (iv) 1-[2-(4-Morpholinyl)ethyl]-3-(1-naphthoyl)indole (Other names: JWH-200).....7200
- (v) 1-Pentyl-3-(1-naphthoyl)indole (Other names: JWH-018 and AM678).....7118

\* \* \* \* \*

Dated: February 24, 2012.

**Michele M. Leonhart,**  
*Administrator.*

[FR Doc. 2012-4982 Filed 2-28-12; 11:15 am]

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1070 (2)

February 25, 2013

Senate Judiciary Committee

**HB 1070**

My name is Wayne Stenehjem, and I'm Attorney General of North Dakota.

Among other duties, I oversee the ND Bureau of Criminal Investigation, the State Crime Lab, and provide legal representation and certain enforcement assistance for state agencies, including the State Department of Health.

Synthetic drug abuse has exploded in North Dakota over the last four years which presents many unforeseen challenges for law enforcement and prosecutors in the State. In 2011, the Legislature scheduled seven chemical groups of synthetic cannabinoids, which were being sold as "incense," and several synthetic cathinones, which were being sold as "bath salts." These substances were sold as allegedly legal alternatives to controlled substances, and, despite their labels stating the products were "not for human consumption," the substances are smoked, snorted, and ingested for the purpose of getting high.

It is widely, perhaps universally, known that these products are sold solely for the purpose of human consumption and ingestion, and that they have psychoactive and mind altering effects. Some of the newer compounds have never been researched or studied on humans so users are test subjects each time they use one of these substances.

When the chemical groups were scheduled, we thought we had taken care of the problem. However, the manufacturers of these substances changed the chemical structure, making the new substances similar to, but different from, the chemical classes that were controlled.

Law enforcement, prosecutors, and medical providers began seeing the same products, labeled with such names as "New Dimension," "Spark," and "100% Pure Evil," now containing a non-controlled synthetic. Reports were coming in of juveniles overdosing on very small amounts of these substances. People who were smoking these substances were combative with police. Users told police they thought they were having a heart attack; they thought their hearts were going to jump out of their chests. Police have also responded to hospital emergency rooms where users have been foaming at the mouth and incoherent.

In June 2012, in the Grand Forks area, two teenagers died and at least one other overdosed on a synthetic cathinone known as 2C-I. In that case, witnesses described the victims as thrashing about and growling and one of the victims was pounding his head into the ground before he stopped breathing.

Unfortunately, because none of these substances are controlled, the distributors of these drugs cannot be charged with any drug trafficking crimes. We have no way, under state law, of prohibiting these dealers from selling these new substances.

These new substances have fallen through the cracks of our current statutes. In the Grand Forks case of the distribution of 2C-I which resulted in the deaths of the two teenagers, the federal government, through the controlled substance analog statute, was able to charge the distributors of 2C-I with drug trafficking offenses. A controlled substance analog is a chemical which is similar to a controlled substance, but is not itself specifically controlled. Drug Enforcement Administration chemists have confirmed that the new synthetic cannabinoids available since the 2011 legislation, including XLR-11, are analogs of the synthetic cannabinoids that are controlled. North Dakota needs a controlled substance analog statute so law enforcement and prosecutors are able to stop the distribution of substances that are similar to controlled substances, yet different enough to be "legal."

In or around March of 2012, and on or about July 12, 2012 two North Dakota consumers reported that they purchased one gram of the product for approximately \$20. "New Dimension" has been shown to contain JWH-018, AKB 48 and URB-754, which are known synthetic cannabinoids, with a likely effect similar to those of THC, a cannabinoid naturally present in cannabis. One of the consumers used a pipe to smoke "New Dimension" and reported to law enforcement that smoking the product gives him "a euphoric relief." The second consumer smoked the product in a "joint" and reported to law enforcement that smoking the product gave him a buzz. The second consumer also allowed another person to smoke some of the joint. Shortly after, this person, a 21 year old male, called 911 in distress, breathing heavily and complaining that he felt as if his heart was going to explode, that his heart was racing and that he needed help. Police and ambulance were dispatched and they found him wandering in a field. He appeared distraught and upset and his face was flushed. He was transported by ambulance to the hospital.

The sale of street drug alternatives has had a damaging and serious effect on the public health in North Dakota and elsewhere. Street drug alternatives are known to cause serious health effects, such as agitation, extreme nervousness, nausea, vomiting, tachycardia (fast, racing heartbeat), dangerously elevated blood pressures, tremors and seizures, hallucinations, severe paranoia, and even death. The products also are extremely habit forming and may cause an intense craving to redose. The products often cause extremely violent behavior, which causes users to harm themselves or others. Users often demonstrate extreme strength, with totally irrational behavior and responses. Over the last several years, there has been a dramatic increase in emergency calls and patients being brought to emergency departments with adverse health effects resulting from ingesting or inhaling a street drug alternative of unknown content.

The street drug alternatives are marketed to target people who are experimenting with "legal highs" or who want to get high without risking positive drug test results. The products are well



known among this group of consumers as a product that may allow them to experience a high legally and without detection.

The legality of the street drug alternatives depends on the chemical structure and composition. The substance may have the same or similar effect on the human body as products banned as controlled substances under N.D.C.C. ch. 19-03.1. However, because this structure can be easily and quickly changed, the street drug alternatives avoid illegality, until regulators or the legislature can include them as a controlled substance and ban them, or prove them to be illegal as an “analogue” under 21 U.S.C. §802(32)(A). The street drug alternatives have shown to be even more dangerous and risky than the substances they attempt to mimic. However, they remain legal until they can be identified and banned by law or regulation.

Working with the Board of Pharmacy, my office drafted this proposed legislation to present to the legislature, but before that I believed we could not wait even three or four months to respond to this epidemic. Reports that I am receiving from law enforcement, the medical community, and citizens generally, tell me that we have an emergency situation here in North Dakota with these synthetics, and so I asked the Board of Pharmacy to adopt emergency rules to add these synthetic substances to the Schedule of Controlled Substances, while waiting to come here with the legislative proposal.



Thank you.



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1070

**HB 1070**  
**Senate Judiciary Committee**

Charlene Schweitzer  
Forensic Scientist  
February 25<sup>th</sup> 2013

The legal designer drug market has exploded in the last four years. The products are marketed as Incense, Potpourri, Bath Salts, and Pond Cleaner or sold on the internet as Research Chemicals and labeled "Not for Human Consumption." However, it is clearly known that they are chemicals that give psychoactive and mind altering effects. The chemicals used to create synthetic drugs are typically shipped into the United States from overseas (China, India, Korea, & Pakistan) where these chemicals are not regulated. They are easy to obtain via the internet and are typically ordered and shipped directly to the distributors that create these products or blends but also can be ordered by individual users. There are many different types of designer drugs and in the last four years the forensic community has seen many different compounds come through in waves. As new laws become enacted, the compounds are constantly changing to circumvent the laws. I will explain the current status and situation of the Cannabinoids, Stimulants, and Hallucinogens as seen by the North Dakota State Crime Laboratory.

***Synthetic Cannabinoids***

Synthetic Cannabinoids are synthetic chemicals that bind to the brain's cannabinoid receptors the same way as THC, the psychoactive ingredient in Marijuana. These compounds are commonly dissolved into a solvent and sprayed onto herbal smoking mixtures. The brain has two cannabinoid receptors referred to as CB1 and CB2. The CB1 receptor is associated with the central nervous system and the CB2 receptor is associated with anti-inflammatory properties. There are hundreds of these synthetic cannabinoid compounds that have been created for medicinal research to seek high affinity for the CB2 receptor for the anti-inflammatory properties without the psychoactive effects from the CB1 receptor but such separation has yet to be found. There are a large amount of synthetic cannabinoid compounds with chemically diverse structure classes so they can be quite different from one another and difficult to control as a whole. These substances have been showing up in the forensic community in waves with the first generation of compounds being the JWH compounds, which we rarely identify in current casework anymore. We are now into the 3<sup>rd</sup> generation wave of synthetic cannabinoids and new compounds keep emerging. In 2011, North Dakota passed SB2119 that placed Synthetic Cannabinoids into seven chemical classes in schedule I of the ND Century Code. This allowed the state to control hundreds of compounds via a generic group definition but the Crime Lab continues to identify new

compounds that fall outside the definition of these seven classes. This bill went into effect Aug 1<sup>st</sup> 2011 and three weeks later, the Crime Lab started identifying new compounds that fell outside of the classes defined in the Century Code. It is being proposed to add an additional class (Tetramethylcyclopropanoylindoles) to the Synthetic Cannabinoids in the Century Code, which includes some of the more common compounds that the Crime Lab is recently identifying in case work. Six other additional synthetic cannabinoid compounds that are being identified in casework and don't fall into any of the classes are also being proposed to be specifically named and added to the Century Code.

***Substituted Cathinones (Bath Salts)***

Substituted cathinone derivatives are based on the natural alkaloid Cathinone that is the active ingredient to the shrub Khat. These compounds are central nervous system stimulants that give users a high similar to Methamphetamine or Cocaine but can become hallucinogenic at very high doses. In 2011, North Dakota scheduled two synthetic cathinone compounds (MDPV and Mephedrone) and the DEA also emergency scheduled these two compounds along with an additional compound (Methylone) on October 21, 2011. The Crime Lab has identified eleven synthetic cathinone compounds in ND, only two of which are currently controlled, and there are numerous others that could potentially be seen. As of June 2012, twenty states have utilized some form of chemical class approach with the substituted cathinones similar to what we did with the synthetic cannabinoids. It is being proposed to do the same with these compounds and have a generic chemical class definition that would encompass these substituted cathinones and would have specific examples listed in the Century Code.

***Hallucinogens (Phenethylamines & Tryptamines)***

Besides the cannabinoids and cathinones there are other designer drugs such as psychedelic hallucinogens which have become increasingly popular. Two groups of hallucinogenic compounds that are encountered are the substituted Phenethylamines and substituted Tryptamines. Some of these compounds have been around for years and are already specifically listed in our law but there new derivatives or analogs that have been showing up more recently in the forensic community.

Psychedelic phenethylamines include numerous compounds that produce extreme hallucinations and mind alterations similar to LSD. On July 9<sup>th</sup> 2012, the DEA added nine of the "2C" compounds (ex: 2C-I, 2C-E, 2C-C) to the Controlled Substances Act but North Dakota has been identifying additional phenethylamine hallucinogen compounds. Two new super potent 2C derivatives (2C-I-NBOMe & 2C-C-NBOMe) have been associated with the two deaths and five other additional overdoses in the Grand Forks area this past summer. Recently I have also heard of other

hospitalizations and deaths possibly associated with these substances from other states. There are hundreds of these substituted phenethylamine compounds that could be encountered and therefore, just like the cannabinoids and substituted cathinones, it is being proposed to add a generic chemical definition of this class of compounds and list specific examples under the definition. Some compounds that would fall into this class are already listed schedule I hallucinogens in the Century Code so they would be moved under this class.

Another group of hallucinogenic compounds is called the substituted tryptamines and are becoming more popular in the designer drug market. These compounds are similar to the natural compounds Psilocyn and DMT, which are already controlled substances. It is being proposed to add a chemical class definition for this class of compounds and list specific examples. Like the Phenethylamines, some compounds may already be listed in the Century Code; therefore some would get moved under the correct class if they meet the definition.

Along with the addition of these generic class definitions, there are an additional four hallucinogenic compounds and two stimulant compounds that are being proposed that will be specifically named and listed.

In closing I must mention that one of the greatest concerns is that there is no consistency in purity or potency of these drugs, and variations in the contents of identical retail packages have been found. There is no consistency in how the drugs are mixed or in how dosages are applied and many times there are numerous compounds found together in one product. It is important for people to understand that with these synthetic drugs, quality control and quality assurance measures are not used so it is highly unlikely that people know exactly what compound or compounds they are actually ingesting. The designer drug market continues to rapidly change and compounds will continue to be identified that may or may not be included in our law. All we can do is to stay informed, aware and continue to monitor the substances being abused so we can protect our youth and citizens of North Dakota.

Thank you.