2015 SENATE JUDICIARY

SB 2100

2015 SENATE STANDING COMMITTEE MINUTES

Judiciary Committee
Fort Lincoln Room, State Capitol

SB 2100
1/14/2015
21942

☐ Subcommittee
☐ Conference Committee

Committee Clerk Signature DPenrose

Minutes: 1,2,3

Sen. Armstrong: We will open the hearing on SB 2100.

Wayne Stenehjem, Attorney General: Support (see attached 1). We have seen a dramatic reduction as the chart shows in samples submitted to the Lab. I'm hearing the same thing from law enforcement and from hospitals. That speaks well of the retailers in ND. We never saw these products being sold in the convenience stores, gas stations in ND; that is unlike the case in all the rest of the country. These compounds are constantly getting tweaked and they try and make some money. The law needs to reflect that the change needs to be made.

Sen. Casper: What percentage of this stuff is produced out of the state and then trafficked into ND.

Wayne Stenehjem: As far as know, we aren't seeing any head shops that are selling it in ND. I would say all of it comes from out of state and that seems to be coming, largely over the internet which is a very difficult thing to get a handle on. They operate interstate, internationally, and this is a national issue that we work with the federal agencies to try and get a handle on it. The internet sale is tough because there are some very robust websites that will sell these and getting through to who is actually running the website is like peeling an onion because there are so many different layers. Now, they are using BitCoin, internet meeting and exchange, which it makes even more difficult to track. We're working constantly on that issue with our federal counterparts.

Sen. Casper: The transaction would be conducted and BitCoin to a website, seller puts it in a FedEx, sends it to buyer's home. How does law enforcement work with that because how do you get in the middle of that.

Wayne Stenehjem: It is very difficult to do that. Unfortunately the way that it often happens, is if there is an injury, overdose or a death and then you have to work back to the way that it started.

Sen. Casper: Do you generally see the packages marketed to younger North Dakotans.

Wayne Stenehjem: Some of the packages are definitely marketed for young people. A lot of young people were going in and buying these for $25-30 per pack, which is per gram and then they are saying, well how dangerous can they be, they aren't illegal, so they must be safe. Of course, they aren't. Being proactive as the legislature has been has helped enormously but we're not done. Then they change the compound and we have to come in and react to it.

Sen. Armstrong: Last session we worked on the bill where it didn't have to be a direct chemical compound, we changed some of the language, so we didn't have to wait two years to add something to the controlled substance act.

Wayne Stenehjem: It works well, but not in every case, which is why this bill is here.

Sen. Armstrong: If you're talking about internet sales and a lot of that is going through the mail, are drug dogs trained to do this. Are we trying to get drug dogs to detect this or is that not feasible.

Wayne Stenehjem: FedEx and some of those companies are very good. They are very willing to work with us on some of those drugs. I don't know how capable a drug dog is on detecting these, but they are very good on marijuana and some of the other drugs that you can detect, that you can train the dog to detect. So often, these are new and different, they aren't always the same.

Sen. Armstrong: Thank you. Further testimony in support.

Mark Hardy, Executive Director, State Board of Pharmacy: Support (see attached 2).

Sen. Armstrong: How are you handling the amendments?

Mark Hardy: Legislative Council should have then. They are still in drafting version of them. We checked with Sen. Anderson and he signed off on the amendments.

Sen. Casper: On the hydrocodone, basically was that going up or down on the schedule.

Mark Hardy: The change was moved from Schedule 3 to Schedule 2. It moved up on the scheduling list. It moved from a substance that wasn't as big as a concern for abuse, to a drug that is a larger concern for abuse. That was done in conjunction with the FDA and DEA, they have a common rule hearing process in which they recommended the change to schedule 2, based on a lot of the abuse concerns that they are seeing across the nation. That was a widespread change and caused a lot of angst within the medical community, as you may or may not be aware. The changes for moving from sched. 3 to sched. 2 for an issuance of a prescription for hydrocodone or the filling of a prescription is a lot different and stricter. It has caused some concerns within the patient population as well. That change occurred a few months ago and I think at this point it has levelled off as far as the impact is concerned.

Sen. Armstrong: Further testimony in support.

Charlene Keller, Forensic Scientist: Support (see attached 3). She showed a chart showing the chemical molecule processes.

Sen. Armstrong: Are there any legitimate products that have this kind of chemical make-up.

Charlene Keller: No.

Sen. Casper: So, you talked about the right side of the chemical structure there, is what they are changing. Does that affect the effect that the drug has on the user, or is it the left side of the compound that maintains purpose of why the user is using the compound and they are just substituting what they can to maintain the left side to get the "high".

Charlene Keller: Basically, is can be on either side of the molecule. They can modify it so very close to the original so as to change one little thing and that has a drastic effect on the body. It doesn't matter necessarily what side of the body. It can have a small effect or a large effect. I think when they are coming up with these compounds; I don't think they really know what effect it's going to have. They just know it beats the legislation. I don't know the effects of these drugs, but I know that a lot of this hasn't been studied or researched.

Sen. Casper: Do you any idea how many variables they could possibly come up with off the base. If the base is producing the drug-like effect which is why they are purchasing the product, is it a limitless amount of variables. I look at the periodic table and all the elements on there, can they just tossing X number of those to produce X number of results.

Charlene Keller: Yes, basically we have been dealing with this for the past four years. I have watched the compounds change and it's drastically and it's ever so slightly. Basically there is a lot of money in this, so the more modifications to make it not "legal", then they know they can get money. It's not necessarily selling it because it produces a good high; it's selling it because this is legal.

Sen. Grabinger: This can't be done in an at-home laboratory. This is being done in a professional laboratory and are we going after that lab, having any success in finding where this stuff is being produced.

Charlene Keller: That is a good question. This is not being made here in ND. This is not even being made in the United States. This is more of an international problem. A lot of these products are coming from China. A lot of people have tied these internet sales to the source in China. I know federal authorities are trying to work with China to stop some of this. There is a lot of money involved in this but it is not being made locally at all.

Sen. Grabinger: But they are able to understand our laws. So when we are trying to fight this, they are making these changes.

Charlene Keller: Yes they are very smart chemists that are making this. They understand the laws, federal and other countries laws very well. We, the United States, are not the only people dealing with this. It is other countries as well.

Sen. Armstrong: Thank you. Further testimony in support. Testimony in opposition. Neutral testimony.

Wayne Stenehjem: If anyone on this committee would like a tour of the crime lab, please let my office know and we will set it up.

Sen. Armstrong: Thank you. We will close the hearing on SB 2100.

2015 SENATE STANDING COMMITTEE MINUTES

Judiciary Committee
Fort Lincoln Room, State Capitol

SB 2100
1/20/2015
22177

☐ Subcommittee
☐ Conference Committee

Committee Clerk Signature DPenrose

Minutes: 1,2

Ch. Hogue: We will take a look at SB 2100. We will have Mark Hardy walk us through the amendments.

Mark Hardy, Exec. Dir. State Board of Pharmacy: Explained the amendments (see attached 1-2) The representative from the Crime Lab walked through the reasons for the amendments and the specific provisions of how they are supposed to be formatted in a way that would best address those substitutions that can be made to the chemical structure of the various compounds. The crime lab put in the various terms in which they identify the specific chemical. They want to specifically put those in there so that it makes it easier for prosecutors and law enforcement identify the compounds they will have an easier way to identify in the law as to what is exactly illegal.

Ch. Hogue: I thought that during last session, when we made amendments to this statute, that we were including the prohibited substances and their derivatives or chemical relatives so that we wouldn't have to continue to amend the statute. Why are we amending it again?

Mark Hardy: The existing statute in there has a chemical group in such a way, and if you go back to Char's picture and showed the chemical structure of the group identified, there was a little bit more specific in that identifying the various substitutions of that. This makes it more about the core chemical structure and the various substitutions. The reason they wanted to take this to the AG's office and the crime lab was because they thought this was more inclusive of future modifications that could be made than the current existing statute. They looked at the state of KS, they made changes like this and they had very good success with preventing future modifications. I think this is a

step to be proactive and in their mind, a better way to define these core chemical structures and to help prevent modifications down the road.

Ch. Hogue: Thank you.

Sen. Armstrong: I move the amendment, 15.8010.01003, Title 02000 with the misspelling error located on page 8, line 15 (a) "subsititution" corrected.

Sen. C. Nelson: Second the motion.

Ch. Hogue: We will take a voice vote. Motion carried. We now have the bill before as amended.

Sen. Armstrong: I move a Do Pass as amended.

Sen. Grabinger: Second the motion.

6 YES 0 NO 0 ABSENT DO PASS AS AMENDED CARRIER: Sen. Casper

1 of 3
TV
1/20/15

15.8010.01003
Title.02000

Prepared by the Legislative Council staff for
Senate Judiciary Committee
January 20, 2015

PROPOSED AMENDMENTS TO SENATE BILL NO. 2100

Page 5, line 25, after the period insert "Other names: Delta-9-tetrahydrocannabinol."

Page 6, line 4, overstrike "Naphthoylindoles. Any compound containing a 3-(1-naphthoyl)indole"

Page 6, overstrike lines 5 through 22

Page 6, line 23, remove "(1)"

Page 6, line 31, replace "by: a substitution" with "in the following ways:

(a) Substitution"

Page 7, line 1, replace "a substitution" with "or

(b) Substitution"

Page 7, line 2, after the second underscored comma insert "or"

Page 7, line 2, replace "A" with "or

(c) A"

Page 7, after line 3, insert:

"(d)"

Page 7, after line 4, insert:

"(e)"

Page 7, line 6, replace "~~[1]~~(a)" with "[1]"

Page 7, line 7, replace "~~[2]~~(b)" with "[2]"

Page 7, line 8, replace "~~[3]~~(c)" with "[3]"

Page 7, line 9, replace "~~[4]~~(d)" with "[4]"

Page 7, line 11, replace "~~[5]~~(e)" with "[5]"

Page 7, line 12, replace "~~[6]~~(f)" with "[6]"

Page 7, line 13, replace "~~[7]~~(g)" with "[7]"

Page 7, line 14, replace "~~[8]~~(h)" with "[8]"

Page 7, line 15, replace "~~[9]~~(i)" with "[9]"

Page 7, line 16, replace "~~[10]~~(j)" with "[10]"

Page 7, line 17, replace "~~[11]~~(k)" with "[11]"

Page 7, line 19, replace "~~[12]~~(l)" with "[12]"

Page 7, line 20, replace "~~[13]~~(m)" with "[13]"

Page 7, line 21, replace "~~[14]~~(n)" with "[14]"

Page 7, line 22, replace "~~[15]~~(o)" with "[15]"

Page 7, line 23, replace "~~[16]~~(p)" with "[16]"

Page 7, line 24, replace "~~[17]~~(q)" with "[17]"

Page 7, line 26, replace "~~[18]~~(r)" with "[18]"

Page 7, line 28, replace "~~[19]~~(s)" with "[19]"

Page 7, line 30, replace "~~[20]~~(t)" with "[20]"

Page 8, line 1, replace "~~[21]~~(u)" with "[21]"

Page 8, line 3, replace "~~[22]~~(v)" with "[22]"

Page 8, line 5, replace "~~[23]~~(w)" with "[23]"

Page 8, after line 6, insert:

"[24] 1-[(N-methylpiperidin-2-yl)methyl]-3-(adamant-1-oyl)indole - Other names: AM-1248.

[25] 1-Pentyl-3-(1-adamantoyl)indole - Other names: AB-001 and JWH-018 adamantyl analog."

Page 8, line 15, replace "by: a substitution" with "in the following ways:

(a) Substitution"

Page 8, line 16, replace "a substitution" with: "or

(b) Substitution"

Page 8, line 17, replace "a" with "or

"(c) A"

Page 8, line 18, replace the first underscored comma with an underscored semicolon

Page 8, line 18, replace "a" with:

"(d) A"

Page 8, after line 19, insert:

"(e)"

Page 8, remove lines 20 and 21

Page 8, line 22, replace "(b)" with "[1]"

Page 8, line 23, after "carboxamide" insert ", APICA, SDB-001, and 2NE1

Page 8, line 24, replace "(c)" with "[2]"

Page 8, line 26, replace "(d)" with "[3]"

Page 8, line 27, after "48" insert "and APINACA"

Page 8, removes lines 28 through 31

Page 9, line 1, replace "(g)" with "[4]"

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Page 10, line 15, replace "(d)" with "[4]"

Page 10, line 17, replace "(e)" with "[5]"

Page 10, line 19, replace "(f)" with "[6]"

Page 27, line 4, underscore "Alfaxalone"

Renumber accordingly

Date: 1/20/2015
Voice Vote # 1

2015 SENATE STANDING COMMITTEE
VOICE VOTE
BILL/RESOLUTION NO. 2100

Senate Judiciary Committee

☐ Subcommittee

Amendment LC# or Description: 15.8010.01003 ; 02000

Recommendation: ☒ Adopt Amendment

☐ Do Pass ☐ Do Not Pass ☐ Without Committee Recommendation

☐ As Amended ☐ Rerefer to Appropriations

☐ Place on Consent Calendar

Other Actions: ☐ Reconsider ☐ _____

Seconded By

Motion Made By Sen. Armstrong Sen. Nelson

Senators	Yes	No	Senators	Yes	No
Ch. Hogue			Sen. Grabinger		
Sen. Armstrong			Sen. C. Nelson		
Sen. Casper					
Sen. Luick					

Total (Yes) _____ No _____

Absent _____

Floor Assignment _____

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

Voice Vote: Motion Carried

Date: 1/20/2015
Roll Call Vote #: 1

2015 SENATE STANDING COMMITTEE
ROLL CALL VOTE
BILL/RESOLUTION NO. 2100

Senate **JUDICIARY** Committee

☐ Subcommittee

Amendment LC# or Description: 15.8010.01003; 02000

Recommendation: ☐ Adopt Amendment
☒ Do Pass ☐ Do Not Pass ☐ Without Committee Recommendation
☒ As Amended ☐ Rerefer to Appropriations
☐ Place on Consent Calendar

Other Actions: ☐ Reconsider ☐ _____

Motion Made By Sen. Armstrong Seconded By Sen. Grabinger

Senators	Yes	No	Senators	Yes	No
Chairman Hogue	✓		Sen. Grabinger	✓	
Sen. Armstrong	✓		Sen. C. Nelson	✓	
Sen. Casper	✓				
Sen. Luick	✓				

Total (Yes) 6 No Ø

Absent Ø

Floor Assignment Sen. Casper

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

1-1

REPORT OF STANDING COMMITTEE

SB 2100: Judiciary Committee (Sen. Hogue, Chairman) recommends **AMENDMENTS AS FOLLOWS** and when so amended, recommends **DO PASS** (6 YEAS, 0 NAYS, 0 ABSENT AND NOT VOTING). SB 2100 was placed on the Sixth order on the calendar.

Page 5, line 25, after the period insert "Other names: Delta-9-tetrahydrocannabinol."

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Page 27, line 4, underscore "Alfaxalone"

Renumber accordingly

2015 HOUSE HUMAN SERVICES

SB 2100

2015 HOUSE STANDING COMMITTEE MINUTES

Human Services Committee
Fort Union Room, State Capitol

SB 2100
3/10/2015
Job #24574

☐ Subcommittee
☐ Conference Committee

Committee Clerk Signature Vicky Crabtree

Explanation or reason for introduction of bill/resolution:

Relating to the scheduling of controlled substances and declare an emergency

Minutes: Testimonies 1-2

Chairman Weisz opened the hearing on SB 2100.

Mark J. Hardy, PharmD, Executive Director of the ND State Board of Pharmacy testified in support of the bill. (See Testimony #1)

6:10
Charlene Keller: Forensic Scientist testified in support of the bill. (See Testimony #2)

12:38
Rep. Porter: As we look at the chart, is there a way to go one above and say if your compound is made up these three components rather than anything other than that is illegal? Or do we have to keep chasing the chemists every two years?

Keller: Are you looking for a catch all?

Rep. Porter: Correct.

Keller: We do have an Analog Act in our state that was added two years ago. It modifies the federal Analog Act saying it has to be chemically similar and give effects in the body similar for each Schedule 1 substance. Then it would be considered a controlled substance analog. It is trickier to pull it off with the newer ones because of not much medical research on the newer compounds. The two prong approach is hard to meet with the Analog Act. Many states have it, but are not using it for the synthetics because of that.

Porter: Does the component inside the criminal code that says if you use the substance in a way that it wasn't intended to be used by the manufacturer, is that something that is held up in the courts? Does that work along with this?

Keller: The inhalant law does cover if you use paint in the way it is not supposed to be used. As far as controlled substances they have to be lifted.

Porter: The availability of the compounds through mail order or internet; so the compound technically in relationship to federal law are legal to produce and manufactured in the U.S., but our law says you cannot have them?

Keller: Our state is ahead of the federal level, but it still is not legal to produce in the U.S. These compounds are being synthesized in China for the most part and distributed through the internet.

Rep. Hofstad: How do you collaborate with other states to try and get a head of these designer drugs that are coming on the market?

Keller: I'm a member of an international organization and it is an e-mail group. Basically, with these synthetics it has been very helpful because we bounce off ideas from each other. I have gotten good contacts throughout the U.S. on what other states are doing and what worked and what didn't.

NO OPPOSITION

Vice-Chair Hofstad closed the hearing on SB 2100.

2015 HOUSE STANDING COMMITTEE MINUTES

Human Services Committee
Fort Union Room, State Capitol

SB 2100
3/10/2015
Job #24599

☐ Subcommittee
☐ Conference Committee

Committee Clerk Signature Vicky Crabtree

Minutes:

Chairman Weisz took up SB 2100.

Rep. Hofstad: I move a Do Pass on SB 2100.

Rep. Seibel: Second.

Chairman Weisz: We are adding one new drug to the schedule 1.

Rep. Porter: It only added two new schedule 1's. The rest is to change the chemical components from the synthetics to the updated version so that we remain ahead of the chemists.

ROLL CALL VOTE: 13 y 0 n 0 absent

MOTION CARRIED

Bill Carrier: Rep. Seibel

Date: 3-10-15
Roll Call Vote #: 1

2015 HOUSE STANDING COMMITTEE
ROLL CALL VOTES
BILL/RESOLUTION NO. 2100

House Human Services Committee

☐ Subcommittee

Amendment LC# or Description: _____

Recommendation: ☐ Adopt Amendment
☒ Do Pass ☐ Do Not Pass ☐ Without Committee Recommendation
☐ As Amended ☐ Rerefer to Appropriations
☐ Place on Consent Calendar

Other Actions: ☐ Reconsider ☐ _____

Motion Made By Rep. Hofstad Seconded By Rep. Seibel

Representatives	Yes	No	Representatives	Yes	No
Chairman Weisz	✓		Rep. Mooney	✓	
Vice-Chair Hofstad	✓		Rep. Muscha	✓	
Rep. Bert Anderson	✓		Rep. Oversen	✓	
Rep. Dick Anderson	✓				
Rep. Rich S. Becker	✓				
Rep. Damschen	✓				
Rep. Fehr	✓				
Rep. Kiefert	✓				
Rep. Porter	✓				
Rep. Seibel	✓				

Total (Yes) 13 No 0

Absent 0

Floor Assignment Rep. Seibel

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

REPORT OF STANDING COMMITTEE

SB 2100, as engrossed: Human Services Committee (Rep. Weisz, Chairman) recommends **DO PASS** (13 YEAS, 0 NAYS, 0 ABSENT AND NOT VOTING). Engrossed SB 2100 was placed on the Fourteenth order on the calendar.

2015 TESTIMONY

SB 2100

#1-1

SB 2100

Wayne Stenehjem
North Dakota Attorney General
January 14, 2015

Last session I was standing here to talk about the epidemic in our state with designer drugs. And that is what it truly was, an epidemic. Here's what I told you last session:

"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.

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

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 re-dose. 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."

Since then, with the help of the laws you passed last session, synthetic drugs are not at the number we were seeing years ago. In November 2012, I issued Cease & Desist Orders against those retailers we knew were selling these products. Since the head shops no longer can sell these substances that are now illegal, it has made it difficult for our children, teens and young adults to obtain these designer drugs.

This is demonstrated by the decreasing number of synthetic drugs being submitted to the Crime Lab in the last two years. When this epidemic was at its peak in 2012, 1366 synthetic drug samples were submitted to the lab. Two years later in 2014, the crime lab identified 164 synthetic drugs samples that were submitted.

The internet is still our biggest obstacle in stopping the distribution of these synthetic chemicals but by having our laws up to date and encompassing the most recent compounds identified has made it more difficult to ship these chemicals to our state since they are illegal under North Dakota's law.

This session it is being proposed to add three new groups to the synthetic cannabinoids section. Charlene Keller, forensic scientist with the ND State Crime Lab, is here to talk about some of the modifications being proposed to encompass some of the new cannabinoid derivatives being identified in case work.

As some of you may have heard, last week there was another overdose death in Grand Forks. This one has been associated with the synthetic opioid Fentanyl, which is a Schedule II substance. It is a very potent painkiller that is more potent than heroin or morphine. There are other areas of the country that see large amount of powder Fentanyl on a regular basis and have had numerous overdoses because of it. There is one analog of fentanyl that we feel should be added to the list of controlled substances this session as Mark Hardy has indicated and that is Acetyl fentanyl. The ND Crime lab has only identified it once but other areas of the country, including Rhode Island and Pennsylvania, have had numerous overdose deaths because of it.

#2-1

State of North Dakota
Jack Dalrynple, Governor

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Mark J. Hardy, PharmD, R.Ph.
Executive Director

Senate Bill No 2100 – Controlled Substances Rescheduling
Senate Judiciary Committee – Fort Lincoln Room
9:30 AM - Wednesday – January 14, 2015

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

Senate Bill 2100 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 adds a few new categories for synthetic spice cannabinoids and compounds within Schedule I controlled substances. The drafting of this bill, specifically the Schedule I substances was done in conjunction with the North Dakota Crime Lab. Charlene Keller, a forensic scientist with the ND Crime Lab is here and will present testimony to explain much of the chemistry and reasons for the new categories listed in this proposed legislation. The intention for these changes is to try to be proactive and ensure that we have future chemical modifications that can be made to these substances, identified as controlled substances. This bill is very lengthy and, we feel, as comprehensive as possible with the information that we have at this time.

I would like to highlight a couple of items to ensure you have an understanding of the approach we utilized in the drafting of this bill.

On page one, line 18 we have schedule Acetylfentanyl, which the state crime lab and federal authorities have identified as a drug of concern.

Starting on page 6 are the new categories for synthetic spice cannabinoids and compounds, which are inclusive of the current cannabinoids. We have moved all specific compounds identified by the state crime lab under the applicable section, to make it clear for those prosecuting or identifying those specific compounds.

It may appear there are many lines struck under the current legislation, but please be aware that each individual compound was moved to the specific applicable new section. Again, this is a strategy to be proactive in the complex nature of these dangerous drugs and to try to keep our citizens safe.

As I indicated earlier, Charlene Keller, a forensic scientist with the ND Crime Lab is here and will present testimony on these changes.

On page 21, line 24 there is the addition of Perampanel, which is a new controlled substance scheduled by DEA since our last legislative session.

On page 22, lines 14-19, you will notice the provisions of hydrocodone being struck from this section and moved to Schedule II. DEA recently lifted the provisions of exemptions for those hydrocodone compounds in schedule III. Hydrocodone products are commonly referred to as Vicodin, Loracet and Norco. They are a drug that is commonly abused.

On page 27, line 4 the addition of Alfaxalone was mistakenly not underlined in this bill, necessitating the re-lettering of the rest of the section. Alfaxalone is another compound that DEA scheduled and we are mirroring.

On page 28, line 22 Suvorexant is also a new drug that fell under schedule IV.

Lastly, we would appreciate your support of the amendments to correct the drafting errors to ensure this legislation is as complete as possible. I would request an emergency clause on the measure to ensure it is effective as soon as possible.

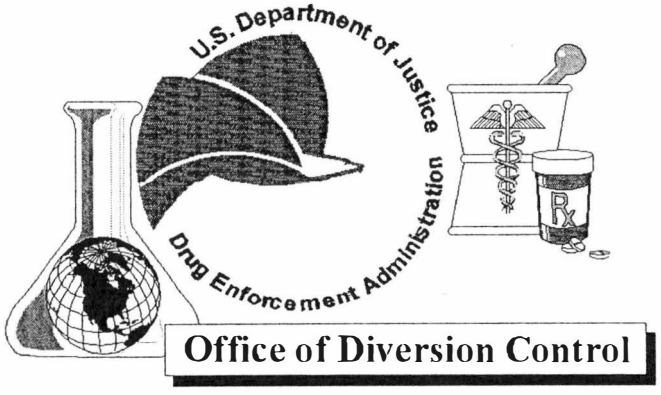
Again, thank you for your time. I will be glad to answer any questions you have at this time.

U.S. Department of Justice
Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

2-3

Lists of:

Scheduling Actions
Controlled Substances
Regulated Chemicals



September 2014

SUBSTANCE *Scheduled under 21 USC 811(h) **Extension of temporary control	PROPOSAL PUBLICATION DATE	FINAL ORDER PUBLICATION DATE	FEDERAL REGISTER CITATION	EFFECTIVE DATE	CSA SCHEDUL
JWH-200 **		02-29-12	77 FR 12201	2/29/2012	I
METHASTERONE (2 ALPHA-17 ALPHA-DIMETHYL-5 ALPHA-ANDROSTAN-17BETA-OL-3-ONE)	11-23-11	07-30-12	77 FR 44456	8/29/2012	III
PROSTANOZOL (17 BETA-HYDROXY-5 ALPHA-ANDROSTANO[3,2-C]PRYAZOLE	11-23-11	07-30-12	77 FR 44456	8/29/2012	III
3,4-METHYLENEDIOXY-N-METHYLCATHINONE (METHYLONE)	10-21-11	04-12-13	78 FR 21818	4/12/2013	I
[1-(5-FLUORO-PENTYL)1H-INDOL-3-YL](2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE(5-FLOURO-UR-144, XLR11)*		05-16-13	78 FR 28735	5/16/2013	I
(1-PENTYL-1H-INDOL-3-YL)(2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE (UR-144)*		05-16-13	78 FR 28735	5/16/2013	I
N-(1-ADAMANTYL)-1-PENTYL-1H-INDAZOLE-3-CARBOXAMIDE (APINACA, AKB48)*		05-16-13	78 FR 28735	5/16/2013	I
LORCASERIN	12-19-12	05-08-13	78 FR 26701	6/7/2013	IV
2-(4-CHLORO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25C-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
2-(4-IODO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25I-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
2-(4-BROMO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25B-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
PERAMPANEL [2-(2-OXO-1-PHENYL-5-PYRIDIN-2-YL-I ,2-DIHYDROPYRIDIN-3-YL)BENZONITRILE]	10-22-13	12-02-13	78 FR 72013	1/2/2014	III
QUINOLIN-8-YL 1-PENTYL-1H-INDOLE-3-CARBOXYLATE (PB–22; QUPIC)*		02-10-14	79 FR 7577	2/10/2014	I
QUINOLIN-8-YL 1-(5-FLUOROPENTYL)-1H-INDOLE-3-CARBOXYLATE (5-FLUORO-PB–22; 5F–PB–22)*		02-10-14	79 FR 7577	2/10/2014	I
N-(1-AMINO-3-METHYL-1-OXOBUTAN-2-YL)-1-(4-FLUOROBENZYL)-1H-INDAZOLE-3-CARBOXAMIDE (AB-FUBINACA)*		02-10-14	79 FR 7577	2/10/2014	I
N-(1-AMINO-3,3-DIMETHYL-1-OXOBUTAN-2-YL)-1-PENTYL-1H-INDAZOLE-3-CARBOXAMIDE (ADB-PINACA)*		02-10-14	79 FR 7577	2/10/2014	I
ALPHA-PYRROLIDINOBUTIOPHENONE (α-PBP)*		03-07-14	79 FR 12928	3/7/2014	I
3-FLUORO-N-METHYLCATHINONE (3-FMC)*		03-07-14	79 FR 12928	3/7/2014	I
4-FLUORO-N-METHYLCATHINONE (4-FMC)*		03-07-14	79 FR 12928	3/7/2014	I
4-METHYL-N-ETHYLCATHINONE (4-MEC)*		03-07-14	79 FR 12928	3/7/2014	I
PENTYLONE*		03-07-14	79 FR 12928	3/7/2014	I
ALPHA-PYRROLIDINOPENTIOPHENONE (α-PVP)*		03-07-14	79 FR 12928	3/7/2014	I
BUTYLONE*		03-07-14	79 FR 12928	3/7/2014	I
NAPHYRONE*		03-07-14	79 FR 12928	3/7/2014	I
4-METHYL-ALPHAPYRROLIDINOPROPIOPHENONE (4-MePPP)*		03-07-14	79 FR 12928	3/7/2014	I
PENTEDRONE*		03-07-14	79 FR 12938	3/7/2014	I
ALFAXALONE (5α-PREGNAN-3α-OL-11,20-DIONE)	03-25-13	02-27-14	79 FR 10985	3/31/2014	IV
TRAMADOL (2-[(DIMETHYLAMINO)METHYL]-1-(3-METHOXYPHENYL)CYCLOHEXANOL)	11-04-13	07-02-14	79 FR 37623	8/18/2014	IV

SUBSTANCE *Scheduled under 21 USC 811(h) **Extension of temporary control	PROPOSAL PUBLICATION DATE	PUBLICATION DATE	FEDERAL REGISTER CITATION	EFFECTIVE DATE	CSA SCHEDULE
SUVOREXANT	02-13-14	08-28-14	79 FR 52143	9/29/2014	IV
HYDROCODONE COMBINATION PRODUCTS	02-27-14	08-22-14	79 FR 49661	10/6/2014	III->II

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

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Acetylfentanyl
(*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide)

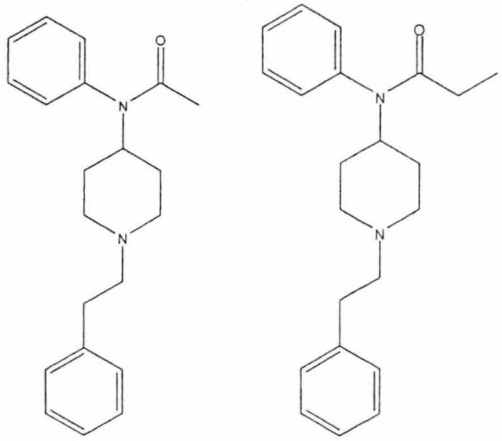
December 2013
DEA/OD/ODE

Introduction:

Acetylfentanyl, similar to the Schedule II opioid fentanyl, is a potent opioid analgesic. Recently, it has been linked to a number of overdose deaths in the northeastern part of the U.S. Acetylfentanyl is not a part of most illicit drug screens and remained undetected in many of these cases. Upon being identified in one death, secondary analyses were performed to confirm the presence of acetylfentanyl in numerous jurisdictions.

Chemistry:

The chemical structure of acetylfentanyl and the Schedule II substance fentanyl are shown below.



Acetylfentanyl Fentanyl

Acetylfentanyl and fentanyl are both synthetic opioids and have similar structures. With one less methyl group attached to the amide group, acetylfentanyl is the N-acetyl version of fentanyl.

Pharmacology:

Acetylfentanyl (EC_{50} = 676 nM), similar to morphine (EC_{50} = 23.6 nM), has been shown to bind to μ-opioid receptors in rat cerebrum membrane preparations. Acetylfentanyl, similar to morphine, has been shown to inhibit the twitch response in electrically stimulated vas deferens preparation. A pharmacology study using acetic acid writhing test showed that acetylfentanyl produces analgesic response in mice 15.7-fold more potent than that of morphine. Potency of acetylfentanyl was about 3-fold less than that of fentanyl in this assay. The ED_{50} (the dose at which 50% of test animals had met the criterion for analgesic response) dose for acetylfentanyl, fentanyl and morphine were 0.021, 0.0061, and 0.33 mg/kg, respectively. Similarly, in another study using tail flick and phenylquinone writhing tests, acetylfentanyl produced analgesic response in mice. Acetylfentanyl has been shown to completely suppress the signs of withdrawal in morphine-dependent monkeys.

Besides analgesia, fentanyl-like substances, similar to other opioid analgesics, produce a variety of pharmacological effects including alteration in mood, euphoria, drowsiness, respiratory depression, suppression of cough reflex, constriction of pupils (miosis), and impaired gastrointestinal motility. Clinical studies evaluating pharmacological effects of acetylfentanyl in humans have not been reported in the scientific literature.

In acute toxicity studies in mice, the LD_{50} (the dose causing death of 50% of test animals) of acetylfentanyl and fentanyl are 9.3 mg/kg and 62 mg/kg, respectively. Significant bleeding in the small intestines of mice was observed in acetylfentanyl-administered mice.

Licit Uses:

There are no published studies as to the safety of acetylfentanyl for human use. There are no commercial medical uses for this substance.

Illicit Uses:

As a μ-opioid receptor agonist, acetylfentanyl may serve as a direct substitute for heroin or other μ-opioid receptor agonist substances in opioid dependent individuals.

Recently, the Centers for Disease Control and Prevention (CDC) issued a health alert to report that between March 2013 and May 2013, 14 overdose deaths related to injected acetylfentanyl had occurred among intravenous drug users (ages between 19 and 57 years) in Rhode Island.

After confirming five overdoses in one county, including a fatality, Pennsylvania asked coroners and medical examiners across the state to screen for acetylfentanyl. This request led to 50 confirmed fatalities and five non-fatal overdoses statewide in 2013.

Control Status

Acetylfentanyl is not currently scheduled under the Controlled Substance Act (CSA). However, if intended for human consumption, acetylfentanyl may be treated as a "controlled substance analogue" under the CSA pursuant to 21 U.S.C §§802(32)(A) and 813.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 202-353-1263, telephone 202-307-7183, or E-mail ODE@usdoj.gov.

Rules - 2013

[Federal Register Volume 78, Number 231 (Monday, December 2, 2013)]
[Rules and Regulations]
[Pages 72013-72016]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2013-28778]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-374]

Schedules of Controlled Substances: Placement of Perampanel into Schedule III

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Deputy Administrator of the Drug Enforcement Administration (DEA) places the substance perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile], including its salts, isomers, and salts of isomers, into schedule III of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule III controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, or possess) or propose to handle perampanel.

DATES: Effective Date: January 2, 2014.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Chief, Policy Evaluation and Analysis Section, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, but they are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purposes of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in **title 21 of the Code of Federal Regulations (CFR) parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

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 established by Congress 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 **[21 U.S.C. 812**(b)] 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 the DEA, who has further delegated this authority to the Deputy Administrator of the DEA. 28 CFR 0.104.

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 the Department of Health and Human Services (HHS),\1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action is based on a recommendation from the Assistant Secretary of the HHS and on an evaluation of all other relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule III controlled substances on persons who handle or propose to handle perampanel.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1995. In addition, because the Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations, for purposes of this document, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

Background

Perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3- yl) benzonitrile] is a new chemical entity with central nervous system (CNS)

[[Page 72014]]

depressant and hallucinogenic properties. On October 22, 2012, the Food and Drug Administration (FDA) approved a new drug application for perampanel as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel will be marketed in the United States under the trade name FYCOMPA[supreg]. Perampanel is a non-competitive AMPA ([alpha]-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid)-type glutamate receptor antagonist. Perampanel was approved in Europe in May 2012 and has been marketed there since July 2012.

HHS and DEA Eight-Factor Analyses

On January 22, 2013, the Assistant Secretary of the HHS provided to the DEA a scientific and medical evaluation and scheduling recommendation entitled "Basis [redacted] the Recommendation for Control of Perampanel and its Salts in Schedule III of the Controlled Substances Act." Following consideration of the eight factors and fin[redacted] related to the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that perampanel be controlled in schedule III of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eight-factor analysis of perampanel pursuant to **21 U.S.C. 811**(c). Electronic copies of these documents are available at www.regulations.gov for easy reference.

Determination to Schedule Perampanel

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Deputy Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Perampanel into Schedule III" on October 22, 2013 (78 FR 62500), which proposed placement of perampanel in schedule III of the CSA. The NPRM provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations on or before November 21, 2013. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposed rule on or before November 21, 2013.

Comments Received

The DEA received two comments on the proposed rule to schedule perampanel. One commenter was in favor of controlling perampanel as a schedule III controlled substance. Another commenter requested that the DEA make the rule effective on the same date as the publication of the final rule.

Support for the Proposed Rule: One commenter supported controlling perampanel as a schedule III controlled substance, as opposed to a schedule II controlled substance, but expressed concern about the unknown effects and abuse potential of this new drug at higher doses. However, the commenter indicated that the controls applicable to schedule III controlled substances are appropriate until there is more available data on perampanel's effects.

DEA Response: The DEA appreciates the comment in support of this rulemaking.

Request to Change Effective Date: One commenter requested that the DEA make this rule effective on the same date as publication to enable physicians and their patients to have access to perampanel as soon as possible and pointed out that the DEA has included an earlier effective date in the final rule for other drugs including zopiclone, pregablin, and ezogabine.

DEA Response: The DEA appreciates the commenter's request, but does not believe an earlier effective date is warranted. As provided in **21 CFR 1308.45**, final orders shall not have an effective date of "less than 30 days from the date of publication in the Federal Register unless the Administrator finds that the conditions of public health or safety necessitate an earlier effective date . . . ." The Administrator finds that the conditions of public health or safety do not necessitate such an earlier effective date in this instance. There are other anti-seizure medications currently available, specifically lacosamide, an anti-epileptic medication that has a similar clinical indication to perampanel. Though the mechanisms of actions of perampanel and lacosamide are different, the indications are very similar. Like perampanel, lacosamide is indicated as an adjunctive therapy for the treatment of partial-onset seizures, and did not have its 30-day implementation period waived. Furthermore, the DEA believes that providing 30 days for this Final Rule to become effective is expeditious and sufficient to allow handlers to obtain the appropriate registration with the DEA and to comply with regulatory requirements for handling schedule III controlled substances.

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of perampanel. As such, the DEA is scheduling perampanel 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 for placing 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 the HHS and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(3), finds that:

1. Perampanel has a potential for abuse less than the drugs or other substances in schedules I and II;

2. Perampanel has a currently accepted medical use in treatment in the United States. Perampanel was approved for marketing by the FDA as an adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older; and

3. Abuse of perampanel may lead to moderate or low physical dependence or high psychological dependence.

Based on these findings, the Deputy Administrator of the DEA concludes that perampanel, including its salts, isomers, and salts of isomers, warrants control in schedule III of the CSA. **21 U.S.C. 812**(b)(3).

Requirements for Handling Perampanel

Upon the effective date of this final rule, any person who handles perampanel is subject to the CSA's schedule III regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement of research, and conduct of instructional activities, of schedule III controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) perampanel, or who desires to handle perampanel, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of January 2, 2014. Any person who is currently engaged in any of the above activities and is not registered with the DEA must

[[Page 72015]]

submit an application for registration and may not continue their activities as of January 2, 2014 unless the DEA has approved that application, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312**.

Security. Perampanel is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93**, pursuant to **21 U.S.C. 823**, **821**, **871**(b) as of January 2, 2014.

Labeling and Packaging. All labels and labeling for commercial containers of perampanel must be in accordance with **21 CFR 1302.03-1302.07**, pursuant to **21 U.S.C. 825**, **958**(e) as of January 2, 2014.

Inventory. Every DEA registrant who possesses any quantity of perampanel on the effective date of this final rule is required to take an inventory of all stocks of perampanel on hand as of January 2, 2014, pursuant to **21 U.S.C. 827**, **958**(e), and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d). Any person who becomes registered with the DEA after January 2, 2014 is required to take an initial inventory of all controlled substances (including perampanel) on hand at the time of registration, pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b). After the initial invento[redacted] every DEA registrant is required to take a biennial inventory of all controlled substances (including perampanel), on hand pursuant to 21 U.S.C. 827, 958(e) and[redacted] accordance with 21 CFR 1304.03, 1304.04 and 1304.11.

Records. All DEA registrants must keep records with respect to perampanel pursuant to **21 U.S.C. 827**, **958**(e) and in accordance with **21 CFR parts 1304**, **130**[redacted] and **1312**, as of January 2, 2014.

Prescriptions. All prescriptions for perampanel or prescriptions for products containing perampanel must comply with **21 U.S.C. 829** and must be issued in accordance with **21 CFR part 1306** as of January 2, 2014.

Importation and Exportation. All importation and exportation of perampanel must be done in accordance with **21 CFR part 1312**, pursuant to **21 U.S.C. 952**, **953**, **957**, and **958** as of January 2, 2014.

Criminal Liability. Any activity involving perampanel not authorized by, or in violation of, the CSA, occurring as of January 2, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

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 performed "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 procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) 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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612), has reviewed this rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to place perampanel, including its salts, isomers, and salts of isomers, into schedule III of the CSA. No less restrictive measures (i.e., non-control or control in a lower schedule) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Perampanel is a new molecular entity, approved by the FDA on October 22, 2012. It was approved in Europe in May 2012, and has been marketed in Europe since July 2012. According to publically available information reviewed by the DEA, perampanel is currently anticipated to enjoy patent protection for at least a decade before generic equivalents may be manufactured and marketed. Accordingly, the number of currently identifiable manufacturers, importers, and distributors for perampanel is extremely small. The publically available materials also specify the readily identifiable persons subject to direct regulation by this final rule. Based on guidelines utilized by the Small Business Administration (SBA), the perampanel manufacturer/ distributor/importer was determined not to be a small entity. Once generic equivalents are developed and approved for manufacturing and marketing, there may be additional manufacturers, importers, and distributors of perampanel, but whether they may qualify as small entities cannot be determined at this time.

There are approximately 1.5 million controlled substance registrants, who represent approximately 381,000 entities. The DEA estimates that 371,000 (97 percent) of these businesses are considered "small entities" in accordance with the RFA and SBA standards. 5 U.S.C. 601(6) and 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that could potentially influence the dispensing rates of new chemical entities, the DEA is unable to determine the number of small entities that might dispense (including administer and prescribe) perampanel (e.g., pharmacies and prescribers).

Despite the fact that the number of small businesses potentially impacted by this final rule could not be determined at this time, the DEA concludes that they would not experience a significant economic impact as a result of this rule. The DEA estimates all anticipated perampanel handlers to be DEA registrants and currently 98 percent of DEA registrants (most of which are small businesses) are authorized to handle schedule III controlled substances. Even if we assume that all of the DEA registrants were to dispense perampanel, (e.g., practitioners prescribe, administer, or dispense the substance, and pharmacies dispense the prescriptions), the costs that they would incur as a result of perampanel scheduling would be

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minimal. Registrants that dispense (but not prescribe) would incur nominal additional security, inventory, recordkeeping, and labeling costs, as they have already established and implemented the required systems and processes to handle schedule III controlled substances. For example, pharmacies and institutional practitioners may disperse schedule II-V controlled substances throughout their stock of non- controlled substances in such a manner as to obstruct theft or diversion of the controlled substances. The inclusion of one additional substance to this system would result in little or no additional burden to such practitioners. In addition, because DEA-registered dispensers must label all schedule II-V controlled substances dispensed, the requirement to label all controlled substances containing perampanel would not impose a significant economic burden upon DEA-registered dispensers (as the infrastructure and materials for doing so would already be in place). Accordingly, compliance would not require significant manpower, capital investments, or recordkeeping burdens.

Registrants who only prescribe perampanel by oral or written prescription would not incur any additional security, inventory, recordkeeping, or labeling costs as a result of this rule, as they would not physically handle perampanel.

Because of these facts, this rule will not result in significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), on the basis of information contained in the "Regulatory Flexibility Act" section above, the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year . . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA 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). This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 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.

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- 2. Amend **Sec. 1308.13** by redesignating paragraphs (c)(11) through (c)(14) as paragraphs (c)(12) through (c)(15) and adding new paragraph (c)(11) to read as follows:

Sec. 1308.13 Schedule III.

* * * * *

(c) * * *

(11) Perampanel, and its salts, isomers, and salts of isomers.. 2261

* * * * *

Dated: November 25, 2013.

Thomas M. Harrigan,
Deputy Administrator.

[FR Doc. 2013-28778 Filed 11-29-13; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-389]

Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II

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 reschedules hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule II controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, conduct chemical analysis with, or possess) or propose to handle hydrocodone combination products.

DATES: This rule is effective October 6, 2014.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, Telephone: (202) 598- 6812.

SUPPLEMENTARY INFORMATION:

Outline

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I. Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, every controlled substance is classified into one of five schedules based upon its potential for abuse, currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause. **21 U.S.C. 812**. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all scheduled substances is published at **21 CFR part 1308**. 21 U.S.C. 812(a).

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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." The Attorney General has delegated this scheduling authority to the Administrator of the DEA. 28 CFR 0.100(b).

The Administrator may initiate the scheduling of any drug or other substance (1) on her own motion; (2) at the request of the Secretary of the Department of Health and Human Services (HHS); or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action was initiated by a petition to reschedule hydrocodone combination products (HCPs) \1\ from schedule III to schedule II of the CSA, and is supported by, inter alia, a recommendation from the Assistant Secretary for Health of the HHS \2\ and an evaluation of all relevant data by the DEA. This final action imposes the regulatory controls and administrative, civil, and criminal sanctions of schedule II controlled substances on any person who handles, or proposes to handle, HCPs.

\1\ Hydrocodone combination products (HCPs) are pharmaceuticals containing specified doses of hydrocodone in combination with other drugs in specified amounts. These products are approved for marketing for the treatment of pain and for cough suppression.

\2\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

II. Background

Hydrocodone was listed in schedule II of the CSA upon the enactment of the CSA in 1971. Public Law 91-513, 84 Stat. 1236, sec. 202(c), schedule II, paragraph (a), clause (1) (codified at **21 U.S.C. 812**(c)); initially codified in DEA regulations at 21 CFR 308.12(b)(1)(x) (36 FR 7776, April 24, 1971) (currently codified at **21 CFR 1308.12**(b)(1)(vi)). At that time, hydrocodone was listed in schedule III of the CSA when formulated with specified amounts of an isoquinoline alkaloid of opium or one or more therapeutically active nonnarcotic ingredients. Pub. L. 91-513, 84 Stat. 1236, sec. 202(c), schedule III, paragraph (d), clauses (3) and (4) (codified at 21 U.S.C. 812(c)); initially codified at 21 CFR 308.13(e) (3) and (4) (36 FR 7776, April 24, 1971) (currently codified at **21 CFR 1308.13**(e)(1) (iii) and (iv)).\3\ Any other hydrocodone single-entity products or combinations of hydrocodone with other substances outside the range of specified doses are listed in schedule II of the CSA.\4\

\3\ Specifically: (iii) "Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with a fourfold or greater quantity of an isoquinoline alkaloid of opium;" (iv) "Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts"

\4\ In the United States there are currently no approved, marketed, products containing hydrocodone in combination with other active ingredients that fall outside schedule III of the CSA. Further, until recently, there were no approved hydrocodone single- entity schedule II products. In October 2013 the FDA approved Zohydro\TM\ ER, a single-entity, extended release schedule II product. Zohydro\TM\ ER was launched on March 3, 2014. Accordingly, all of the historical data regarding hydrocodone from different national and regional databases that support this rule should refer to HCPs only, regardless of whether the database utilizes the term "hydrocodone" or "hydrocodone combination products."

III. Determination To Transfer Hydrocodone Combination Products (HCPs) to Schedule II

Pursuant to **21 U.S.C. 811**(a), proceedings to add a drug or substance to those controlled under the CSA, or to transfer a drug between schedules, may be initiated on the petition of any interested party. The DEA received a petition requesting that HCPs be controlled in schedule II of the CSA. In response, in 2004, the DEA submitted a request to the HHS to provide the DEA with a scientific and medical evaluation of available information and a scheduling recommendation for HCPs, pursuant to 21 U.S.C. 811 (b) and (c). In 2008, the HHS provided to the DEA its recommendation that HCPs remain controlled in schedule III of the CSA. In response, in 2009, the DEA requested that the HHS re-evaluate their data and provide another scientific and medical evaluation and scheduling recommendation based on additional data and analysis.

On July 9, 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144, 126 Stat. 993) (FDASIA). Section 1139 of the FDASIA directed the Food and Drug Administration (FDA) to hold a public meeting to "solicit advice and recommendations" pertaining to the scientific and medical evaluation in connection with its scheduling recommendation to the DEA regarding drug products containing hydrocodone, combined with other analgesics or as an antitussive. Additionally, the Secretary was required to solicit stakeholder input "regarding the health benefits and risks, including the potential for abuse" of HCPs "and the impact of up-scheduling these products." Accordingly, on January 24 and 25, 2013, the FDA held a public Drug Safety and Risk Management Advisory Committee (DSaRM) meeting, at which the DEA made a presentation.\5\ The DSaRM Committee included members with scientific and medical expertise in the subject of opioid abuse, and a patient representative. Members included

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representatives from the National Institute on Drug Abuse (NIDA) and the Centers for Disease Control (CDC). There was also an opportunity for the public to provide comment. The DSaRM voted 19 to 10 in favor of recommending that HCPs be placed into schedule II. According to the FDA, 768 comments were submitted to the FDA by patients, patient groups, advocacy groups, and professional societies.

\5\ The DEA presentation is available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagmentadvisorycommittee/ucm346941.pdf.

Upon evaluating the scientific and medical evidence, along with the above considerations mandated by the FDASIA, the HHS on December 16, 2013, submitted to the Administrator of the DEA its scientific and medical evaluation entitled, "Basis for the Recommendation to Place Hydrocodone Combination Products in Schedule II of the Controlled Substances Act." Pursuant to **21 U.S.C. 811**(b), this document contained an eight-factor analysis of the abuse potential of HCPs, along with the HHS recommendation to control HCPs in schedule II of the CSA.

The HHS stated that the comments received during the open public hearing and submitted to the docket, and the discussion of the DSaRM members of the FDA DSaRM meeting provided support for its conclusion that: (1) Individuals are taking HCPs in amounts sufficient to create a hazard to their health or to the safety of

other individuals or to the community; (2) there is significant diversion of HCPs; and (3) individuals are taking HCPs on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs. The HHS stated that it gave careful consideration to the fact that the members of the DSaRM voted 19 to 10 in favor of rescheduling HCPs from schedule III to schedule II under the CSA. The HHS considered the increasing trends, the public comments, the recommendation of the DSaRM, the health benefits and risks, and the information available about the impact of rescheduling, and concluded that HCPs have high potential for abuse.

[redacted]After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II" which proposed to reschedule HCPs from schedule III to schedule II of the CSA. 79 FR 11037, Feb. 27, 2014. Both the DEA and HHS eight-factor analyses, as well as the DEA's Economic Impact Analysis (EIA), were made available in their entirety in the public docket for this rule (Docket No. DEA-389) and are available at http://www.regulations.gov/#!docketDetail;D=DEA-2014-0005 under "Supporting and Related Material." The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by March 31, 2014. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before April 28, 2014. The DEA specifically solicited comments on the economic impacts of rescheduling with a request that commenters describe the specific nature of any impact on small entities and provide empirical data to illustrate the extent of such impact.

IV. Comments Received

The DEA received 573 comments on the proposed rule to reschedule HCPs. Fifty-two percent (52%) (298 comments) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. Forty- one percent (41%) (235 comments) opposed rescheduling HCPs into schedule II. Seven percent (7%) (40 comments) did not take a definitive position regarding rescheduling of HCPs.

Comments were submitted by a variety of individuals, including among others: Federal and State Government officials, manufacturers, distributors, pharmacies, surgeons, emergency physicians, dentists, physician assistants, nurse practitioners, pharmacists and pharmacy students, ultimate users of HCPs, and members of the general public.6 7 The DEA also received comments from a number of national and regional trade associations with memberships comprised of manufacturers and distributors, pharmacists, pharmacies, physicians, pain specialists, doctors of optometry, physician assistants, nurse practitioners, and long term care facilities (LTCFs). In addition, the DEA received comments from patient advocacy groups. The 5 commenter categories with the most submissions were physicians (13%; 73 comments); mid-level practitioners \8\ (5%; 31 comments); pharmacists and pharmacy students (21%; 122 comments); the general public (44%; 250 comments); and ultimate users (6%; 35 comments).

\6\ The term "ultimate user" means a person who has lawfully obtained, and who possesses, a controlled substance for his own use or for the use of a member of his household or for an animal owned by him or by a member of his household. **21 U.S.C. 802**(27).

\7\ Comments from the "general public" are distinguished from those submitted by "ultimate users" when the commenter did not specifically indicate in their comment that they personally use HCPs.

\8\ The term "mid-level practitioner" means an individual practitioner, other than a physician, dentist, veterinarian, or podiatrist, who is licensed, registered, or otherwise permitted by the United States or the jurisdiction in which he/she practices, to dispense a controlled substance in the course of professional practice. **21 CFR 1300.01**(b).

As discussed above, 52% of all commenters (298 of 573 comments) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. The majority of those supporting the rule were members of the general public and physicians. Comments submitted by the general public comprised 62% of the total 298 comments that supported, or supported with qualification, the rescheduling. Seventy-four percent (74%) (184 of 250 comments) of all comments submitted by the general public were in support, or supported with qualification, the rescheduling. Comments by physicians comprised 14% of the total 298 comments that supported or supported with qualification rescheduling. Fifty-six percent (56%) (41 of 73 comments) of all comments submitted by physicians were in support, or supported with qualification, rescheduling.

[redacted]orty-one percent (41%) of commenters (235 of 573 comments) opposed the proposal to reschedule HCPs from schedule III to schedule II of the CSA. The majority of those opposed to rescheduling HCPs were pharmacists, pharmacy students, and ultimate users. Pharmacists and pharmacy students comprised 31% of the total 235 comments submitted in opposition to the rule. Sixty percent (60%) (122 comments) of all comments submitted by pharmacists and pharmacy students were in opposition to the rule. Comments from ultimate users comprised 14% of the total 235 comments in opposition to the rule. Ninety-one percent (91%) (32 of 35 comments) of all comments submitted by ultimate users were in opposition to rescheduling.

Further discussions of these comments are included below.

A. Support of the Proposed Rule

Two hundred ninety-eight commenters (52%) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. Forty- one percent (41%) of commenters opposed controlling HCPs in schedule II, and 7% of commenters

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did not have a clearly defined position either in support or in opposition to the rescheduling. The majority of those supporting the rule were members of the general public (62%) and physicians (14%), with 74% of comments from the general public supporting, or supporting with qualification, and 56% of comments from physicians supporting, or supporting with qualification, making HCPs schedule II controlled substances. Manufacturers, pharmacists, mid-level practitioners, pharmacy students, and trade associations also expressed support for the rule. Of all comments submitted, in support and opposition, 40% of pharmacists, 9% of ultimate users, and 78% of the general public were in support.

The State Attorney General and a U.S. Senator from the State with last year's highest per capita rate of prescription drug overdose in the nation wrote in strong support of rescheduling HCPs. The State Attorney General wrote that, "This reclassification is not only justified given the high abuse and addiction potential of hydrocodone prescription painkillers * * *, it is necessary to combat the drug abuse epidemic that is destroying so many [ ] communities. I urge you to proceed with your rulemaking without delay. The abuse of hydrocodone is an urgent problem that necessitates urgent action." The U.S. Senator wrote that, "rescheduling hydrocodone combination drugs would be a tremendous step forward in the fight to curb the prescription drug abuse epidemic that has ravaged * * * our country. It will help prevent these highly addictive drugs from getting into the wrong hands and devastating families and communities * * *. I urge the DEA to move quickly in finalizing its regulations so that we are able to save hundreds of thousands of lives."

Two U.S. Senators from two other States, wrote a joint comment in support of rescheduling, stating that: "As members of the Judiciary Committee and senators from states hit particularly hard by the opioid epidemic, we are well aware of the alarming rates of diversion and prescription drug abuse," and "we fully support DEA's efforts to combat this nationwide public health crisis." All three Senators expressed their desire that patients maintain access to legitimate care.

A major component of the rescheduling of HCPs was to evaluate their abuse potential as required under **21 U.S.C. 812**(b)(2). Many commenters indicated support for controlling HCPs in schedule II based on the scientific evidence demonstrating the high abuse potential of HCPs, evidence that HCPs may lead to severe psychological or physical dependence, history and current pattern of abuse, significance of abuse, and risk to the public health and safety. Of the total 47 commenters who referenced the scientific, medical, and epidemiological data that was used to support the statutory requirement under 21 U.S.C. 812(b)(2) for control of HCPs in schedule II of the CSA, 29 agreed with the data used to support control of HCPs in schedule II. Nineteen commenters specifically discussed the eight-factor analysis that was conducted in support of rescheduling HCPs into schedule II. Ten of those 19 commenters were in agreement with the DEA's analysis. Nine of the commenters who cited the DEA's eight-factor analysis indicated that the presented evidence was congruent with the requirements for placing a drug or other substance into schedule II of the CSA. (One commenter, while in agreement with the conclusion of the eight-factor analysis, did not favor rescheduling HCPs.)

[redacted]ommenters generally agreed that there is psychological and physical dependence associated with HCPs that support placement into schedule II. For example, one commenter stated that rescheduling HCPs from schedule III to schedule II "would be in the best interest of the general public" because he has personally witnessed the increase in abuse of prescription pain medication over the course of his 45-year career as a pharmacist. Additional supportive comments included that the mechanism of action of hydrocodone is identical to oxycodone and morphine, both in schedule II as combination and single-entity products. Some commenters indicated that lower doses of hydrocodone in HCPs do not lower abuse and therefore agreed with the transfer to schedule II. Other commenters mentioned that HCPs are metabolized to hydromorphone, a schedule II opioid, and also have similar mechanisms of action to other schedule II opioids including oxycodone, morphine, and fentanyl, suggesting that abuse potential would be comparable. Some of the commenters indicated that HCPs are more likely to be abused due to their greater availability.

Many of the commenters cited one of their primary reasons for supporting the rule was that it would lead to tighter regulation of HCP prescriptions. For example, one commenter stated: "Hydrocodone combination products should not be available with multiple refills on a single prescription and need to be prescribed more cautiously." Similarly, another commenter stated: "Rescheduling HPCs [sic] would directly address the problem of 'leftover' pills in parents [sic] medicine cabinets, and would keep kids safe. Furthermore, lowering the quantity a doctor can prescribe will decrease the number of drugs that are sold on the street, which will in turn decrease crime and decrease HCP abuse overtime [sic]."

Many of the commenters wrote of their personal experiences with loved ones who suffer or had suffered with abuse and addiction, including many youths and yo adults who have tragically died as a result of HCPs or other prescription opioids. The commenters wrote that the path to abuse and addiction was varied--someti beginning with a practitioner prescribing HCPs, and other times by recreational use of pills that were available for them to access as a result of practitioner overprescribing. Many of these commenters believe that controlling HCPs as a schedule II controlled substance will impose controls necessary to prevent the abuse and diversion of HCPs.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

B. Request for Extended Comment Period

The DEA received two comments requesting that the DEA reopen the period for public comment. One of the commenters specifically requested that the comment period be reopened for a minimum of 180 days. The stated justification of one of the commenters was that "[t]he current period is utterly inadequate to large segments of the population who have had no meaningful notice, have extremely limited internet access in small time periods through use of computers at public libraries and are particularly at risk from harm if this rule is adopted." Both requests for extended comment periods were accompanied by meaningful comment along with the request for extension.

DEA response: The Administrative Procedure Act does not set a minimum length of time for public comment. 21 U.S.C. 553; Phillips Petroleum Co. v. U.S. E.P.A., 803 F.2d 545, 558-59 (10th Cir. 1986) (upholding the EPA's refusal to extend the 45-day comment period on an NPRM, noting that courts have uniformly upheld comment periods of 45 days or less) (internal citations omitted). However, both Executive Orders 12866 and 13563 provide that agencies should afford the public a comment period of at least 60 days. The DEA published in the Federal Register the NPRM proposing to reschedule HCPs into schedule II of the CSA on February 27, 2014. 79 FR 11037. The

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DEA provided 60 days for interested persons to submit written comments (either online or through the mail) on the proposal. The comment period closed April 28, 2014. Seven hundred twenty-four submissions on the associated docket at http://www.regulations.gov were submitted by the close of the comment period. Several paper submissions duplicating electronic submissions were received via the mail as well. (The 724 number differs from the finalized number of 573 comments received because, as alluded to above, many commenters submitted multiple, duplicate submissions. Multiple submissions of exactly identical comments submitted by the same person or entity are considered by the DEA as only a single, submitted comment.) Based on the following considerations, the DEA declines to reopen the period for additional public comment.

The Federal Register is published daily, Monday through Friday, except official holidays, by the Office of the Federal Register, National Archives and Records Administration, under the Federal Register Act (44 U.S.C. chapter 15). Section 7 of the Federal Register Act (44 U.S.C. 307) provides that publication in the Federal Register constitutes constructive notice to persons subject thereto or affected thereby. The Federal Register is published in paper and on microfiche. It is also available online at no charge at http://www.gpo.gov/fdsys/.

The NPRM was also available on http://www.regulations.gov to enable the public to conveniently access the proposal and the supporting materials. Of additional consideration, on the same day as publication in the Federal Register, the DEA issued a press release stating that the Administration had published in the Federal Register an NPRM to move HCPs from schedule III to schedule II (available at http://www.justice.gov/dea/divisions/hq/2014/hq022714.shtml). The press release advised individuals where a complete copy of the NPRM could be obtained as well as how they could submit comments in response to the proposal. The DEA accepted written comments submitted either through Regulations.gov or through the mail.

In accordance with the Administrative Procedure Act, the DEA's published NPRM included "the terms or substance of the proposed rule" and "a description of the subject and issues involved." 5 U.S.C. 553(b)(3). The quality and quantity of the responses received in response to the published NPRM, as well as the variety of respondents, including those advocating on behalf of persons residing in LTCFs and other populations that may potentially feel distributional regulatory impacts, demonstrate to the DEA that there has been an adequate opportunity for meaningful public participation by interested persons in accordance with the Administra Procedure Act. 5 U.S.C. 553(c); Idaho Farm Bureau Fed'n v. Babbitt, 58 F.3d 1392, 1404 (9th Cir. 1995) (holding that comments discussing the proposed action a supporting data were evidence that the public had obtained and reviewed the information and thus adequate opportunity for public comment had been given).

The DEA notes that the submission by a nurse located in Australia shows that the published NPRM was widely read and reviewed. In addition, those commenters requesting additional time for comment accompanied their request for an extension with substantial comment on the rule. This demonstrates to the DEA that adequate notice and opportunity for meaningful comment was provided by the DEA on this rulemaking.

C. Clarification of Affected Drugs and Substances

The DEA received some comments, though limited in number, indicating it would be helpful to provide detailed discussion of what products are affected by this rule. One commenter specifically requested clarification as to whether the action would apply to cough syrups that contain hydrocodone. The second commenter requested the DEA not change the schedule of ZohydroTM ER. The third commenter requested that Zogenix, the manufacturer of ZohydroTM ER, be "allow[ed] to bring their new drug to market."

DEA response: This rulemaking action affects hydrocodone combination products, which are those substances described in **21 CFR 1308.13**(e)(1) (iii) and (iv). All other products containing hydrocodone are already controlled in schedule II of the CSA and are not impacted by this action. ZohydroTM ER does not meet the definition of either 21 CFR 1308.13(e)(1) (iii) or (iv); it is currently a schedule II controlled substance under **21 CFR 1308.12**(b)(1)(vi) and is not affected by this action.

Other than ZohydroTM ER, all pharmaceuticals containing hydrocodone currently on the market in the United States are HCPs and are subject to this rulemaking. Hydrocodone is the most frequently prescribed opioid in the United States with nearly 137 million prescriptions for HCPs dispensed in 2013. IMS Health, National Sales PerspectiveTM (NSP). There are several hundred brand name and generic hydrocodone products marketed with the most frequently prescribed combination being hydrocodone and acetaminophen (e.g., Vicodin[supreg], Lortab[supreg]). Currently marketed HCPs approved as cough suppressants include Hycodan[supreg], Mycodone[supreg], Tussionex[supreg], Pennkinetic[supreg], Tussigon[supreg], and several generics.

D. Opposition to the Proposed Rule

Two hundred thirty-five commenters (41% of all commenters) opposed the proposal to reschedule HCPs from schedule III to schedule II of the CSA. Many comments submitted in opposition came from pharmacists, including pharmacy school students/interns (31%); the general public (23%); and ultimate users (14%). Of all comments submitted, in support and in opposition, 60% of pharmacists were opposed; 22% of the general public were opposed; and 91% of ultimate users were opposed. These commenters opposed the rescheduling HCPs for a variety of reasons. The comments in opposition can be grouped in the following general categories: (1) Concerns over the DEA's authority to reschedule HCPs; (2) concerns over prescribing practices; (3) concerns regarding patient access to medicine; (4) concerns regarding impacts at LTCFs; (5) concerns that rescheduling HCPs will not prevent abuse or diversion; (6) concerns that rescheduling HCPs will increase provider and pharmacist workload; (7) concerns regarding economic impacts to manufacturers, distributors, pharmacies, physicians, and ultimate users; (8) concerns that alternatives to rescheduling had not been explored and/or implemented first; and (9) concerns about the amount of time to comply with the rule. Each of these general categories is addressed below.

1. Authority To Control Drugs or Substances

a. DEA's Authority To Schedule Substances

One commenter questioned the DEA's general authority to schedule drugs.

DEA response: Recognizing the need for a high level of scrutiny over controlled substances due to their potential for abuse and danger to the public health and sa Congress established a closed system of distribution for all controlled substances with the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970. See H.R. Rep. No. 91-1444, 1970 U.S.C.C.A.N. at 4566. The DEA

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implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. 28 CFR 0.100. 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 [**21 U.S.C. 812**(b)] 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 the DEA. The DEA's authority to implement and enforce the CSA, including adding to the schedules, has been repeatedly recognized and upheld in the Courts. E.g., U.S. v. Alexander, C.A.9 (Cal.) 1982, 673 F.2d 287 (1982), cert. denied, 459 U.S. 876 (Congress' delegation to Attorney General of authority to reclassify controlled substances is constitutional); U.S. v. Roya, C.A.7 (Ill.) 1978, 574 F.2d 386, cert. denied, 439 U.S. 857 (finding no merit to the claim that the addition and reclassification of amobarbital and phenmetrazine as schedule II controlled substances by the Attorney General was an unconstitutional delegation of authority under separation of powers doctrine); U.S. v. Kinder, C.A.5 (Tex.) 1991, 946 F.2d 362, cert. denied, 503 U.S. 987, cert. denied, 504 U.S. 946, rehearing denied, 505 U.S. 1238 (Attorney General followed proper procedures in reclassifying methamphetamine as schedule II controlled substance, pursuant to the CSA; Attorney General properly delegated his authority to the Director of the Bureau of Narcotics and Dangerous Drugs (BNDD) who then reclassified methamphetamine).

b. Conflict With Other Federal Law

One commenter questioned whether the rescheduling action would have illegal discriminatory effects, and "violate laws against disability and age discrimination." This same commenter also asserted without premise that the rescheduling action could potentially conflict with parts of the Affordable Care Act and "deprivation of rights under color of authority."

DEA response: Executive Order 12866 of September 30, 1993, "Regulatory Planning and Review," and Executive Order 13563 of January 18, 2011, "Improving Regulation and Regulatory Review," direct Federal agencies to assess costs and benefits of available regulatory alternatives and, if the regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). Paragraph (b)(1) of section 1 of Executive Order 12866 specifically directs Federal agencies to "avoid regulations that are inconsistent, incompatible, or duplicative with its other regulations or those of other Federal agencies." The DEA has reviewed the impacts of this scheduling action against the principles edified by Executive Orders 12866 and 13563 and finds no basis that it would have illegal discriminatory effects, or "violate laws against disability and age discrimination."

c. Factors Determinative of Control

Twenty-six commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns regarding the eight-factor analyses. Twenty-four commenters believed that the eight-factor analyses did not support rescheduling into schedule II and that HCPs should remain in schedule III. Two commenters believed that HCPs should be rescheduled into a lower schedule than schedule III. (One commenter stated that HCPs should be down-scheduled into schedule V and made over-the-counter for those 21 years and older.)

i. Evaluation of Abuse Potential of HCPs and Data Used To Support Placement of HCPs into Schedule II of the CSA

Eighteen commenters expressed disagreement about the data that was used to support the statutory requirement under **21 U.S.C. 811**(c) and **812**(b)(2) for placement into schedule II of the CSA. Some of these commenters stated that the available data are limited and do not support rescheduling HCPs into schedule II. Some commenters indicated that there was no scientific consensus in support of moving HCPs from schedule III to schedule II.

Many of the comments in opposition to the proposed scheduling action were statements by ultimate users of HCPs that HCPs are not abused by patients with legitimate prescriptions. Some of the commenters stated that the small amounts of hydrocodone in HCPs have never contributed to addiction and acetaminophen in HCPs would actually decrease abuse rates. Commenters suggested that abuse potential of HCPs is lowered or negated by the fact that it is often used with other substances such as alcohol. Some commenters supported their assertions with statements that deaths are extremely rare with HCPs.

DEA response: The DEA conducted a comprehensive evaluation of epidemiological, diversion, pharmacological, and pharmacokinetic data to conclude that HCPs have a high abuse potential. All of the data was reviewed collectively, and the data supports the finding that HCPs have a high abuse potential similar to other schedule II controlled substances, such as oxycodone products. The DEA's decision to reschedule HCPs from schedule III to schedule II is also supported by the HHS review and the FDA's DSaRM recommendation.

The DEA disagrees that there is a lack of scientific consensus among scientific experts. Some commenters, in support of their dissenting opinions, cited some selective information presented in the briefing document for the FDA's DSaRM meeting in January 2013. It should be noted that the DSaRM members received the selected information cited by the commenters, and, upon deliberating extensively on all the available data voted 19 to 10 in favor of rescheduling HCPs from schedule III to schedule II. The DEA's determination of the appropriate schedule under the CSA in which to place HCPs is based on a comprehensive review of all available data, rather than selected portions of available data, and the DEA did in fact review and consider the selected information presented by the commenters. The DEA also considered the HHS scientific and medical evaluation and scheduling recommendations.

The DEA finds that the scientific, medical, and epidemiological data are robust and support rescheduling HCPs into schedule II of the CSA. Various drug abuse indicators for HCPs indicate that HCPs are widely diverted and abused at rates largely similar to that of oxycodone products (schedule II). The data indicate that HCPs have an abuse potential similar to schedule II opioid analgesics such as oxycodone and their abuse is associated with severe psychological or physical dependence. Abuse of HCPs is also associated with large numbers of individuals being admitted to addiction treatment centers. Individuals are taking these drugs in sufficient quantities to create a hazard to their health, and abuse of HCPs is associated with large numbers of deaths. Further, data from several different drug abuse monitoring databases support the conclusion that HCPs have a high potential for abuse similar to other schedule II opioid analgesics.

Contrary to the views expressed by some commenters, the review by the DEA and HHS of all the relevant data found that HCPs are abused at high rates and have high dependence potential as indicated by the data reported by the National Survey on Drug Use and

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Health (NSDUH), Monitoring the Future (MTF), National Poison Data System (NPDS), Drug Abuse Warning Network (DAWN), and Treatment Episode Data Set (TEDS). There have been large numbers of deaths and emergency department visits associated with abuse of HCPs. In addition, the data indicate that HCPs and oxycodone products have similar abuse potential. Based on these considerations, the DEA believes that the high abuse and dependence potential and harm associated with HCPs support rescheduling into schedule II of the CSA.

Contrary to statements made by some ultimate users, even low doses of HCPs have the potential for adverse impacts on the public health and safety. According to the CDC, while an estimated 80% of patients who are prescribed opioids are prescribed low doses (<100 mg morphine equivalent dose per day) by a single practitioner, these patients account for an estimated 20% of all prescription drug overdoses.\9\ (An estimated 10% of patients who are prescribed opioids are prescribed high doses (>=100 mg morphine equivalent dose per day) by single prescribers. These patients account for an estimated 40% of all prescription opioid overdoses. An estimated 10% of patients are patients who seek care from multiple doctors and are prescribed high daily doses of opioids. They account for another 40% of all opioid overdoses.) Id.

\9\ Centers for Disease Control, CDC Grand Rounds: Prescription Drug Overdoses--a U.S. Epidemic, 61(01) Morbidity and Mortality Weekly Report (MMWR) 10 (2012) (internal citations omitted) available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm.

After careful consideration of relevant data, the DEA finds that HCPs have abuse potential supporting placement into schedule II.

ii. Criteria for Abuse

One commenter wanted the DEA to draw distinctions among abuse, addiction, and dependence. A second commenter objected to the DEA's consideration of "individuals taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs" as a criterion of abuse.

DEA response: As noted by researchers, "[t]here is no agreement between researchers for terms such as drug abuse, psychological dependence, drug dependence and drug addiction," and that, "[o]ften these terms are used interchangeably." \10\ The DEA is aware that the most recent version of the Diagnostic and Statistical Manual, the DSM- V, released in 2013, removed the distinction between abuse and dependence for diagnostic purposes, and replaced them with a combined single disorder called "substance use disorder." However, the DEA derives authority from the CSA, and when acting under its authority must speak under the terms and conditions imposed by it. The CSA does not define "abuse" in terms of the DSM; in fact it does not define the term at all. The CSA uses terms such as "potential for abuse," "pattern of abuse," and "significance of abuse." E.g., **21 U.S.C. 811** and **812**.

\10\ Laxmaiah Manchikanti, MD et al., National All Schedules Prescription Electronic Reporting Act (NASPER): Balancing Substance Abuse and Medical Necessity, 5 Pain Physician 294, 299, n.3 (2002).

One looks first to the face of a law to understand its meaning, and "[i]f the statute's meaning is plain and unambiguous, there is no need for further inquiry." United States v. Fisher, 289 F.3d 1329, 1337-38 (11th Cir.2002) (internal quotation marks and citation omitted). However, if the language is ambiguous, the relevant legislative history may be used to aid in understanding meaning. United States v. Dodge, 597 F.3d 1347, 1352 (11th Cir. 2010). The legislative history of the CS suggests four factors that may be considered in determining whether a particular drug or substance has a "potential for abuse," including whether individuals ar 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.\11\ Accordingly, the DEA uses this as one factor in determining a substance's potential for abuse.

\11\ As provided in the CSA's legislative history:

* * * [A] substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect if: (1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or (2) There is a significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or (3) 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 (4) 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.

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

"Addict" is defined by the CSA as a person who "habitually uses any narcotic so as to endanger the public morals, health, safety, or welfare, or who is so far addicted to the use of narcotic drugs as to have lost the power of self-control with reference to his addiction." **21 U.S.C. 802**(1). The DEA uses this definition for the terms "addict" and "addiction."

iii. Appropriate Drug Comparator

One commenter asserted that HCPs were not compared to appropriate reference drugs and have lower abuse ratios and abuse potential than schedule II oxycodone combination products. Another commenter expressed the opinion that HCPs are substantially cheaper than oxycodone products which would affect drug selection as opposed to the notion that HCPs have more addiction potential. The commenters did not provide any appropriate alternative comparison drug for HCPs.

DEA response: HCPs were compared to oxycodone products, currently schedule II controlled substances, to evaluate abuse potential. The DEA, in agreement with the HHS review, considers the comparison of HCPs to oxycodone products appropriate due to similarities between their pharmacological properties, therapeutic uses and patterns, as well as market history. In their eight-factor analysis, the FDA noted that it is not always possible to identify an "appropriate opioid comparator in Schedule III." The FDA went on to state that: "While FDA considered codeine as a potential comparator, it was deemed inappropriate for several reasons * * *. Given the absence of an appropriate Schedule III comparator, FDA focused its analyses on comparing the abuse liability of hydrocodone combination products (Schedule III) with oxycodone products (Schedule II)."

With regard to the comment about the lower costs of HCPs contributing to its high abuse potential, it is important to note that abuse potential of a given drug is also influenced by various other factors (e.g., pharmacological properties, ease of availability, etc.). Additionally, actual abuse data comparing HCPs and oxycodone combination drugs indicate that the abuse potential between the two drugs is similar. Contrary to the views expressed by some commenters, the review by the DEA of all the relevant data found that HCPs are abused at high rates and have high dependence potential as indicated by the data

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reported by the NSDUH, MTF, NPDS, DAWN, and TEDS. There have been large numbers of deaths and emergency department visits associated with abuse of HC Based on these considerations, the DEA believes that the high abuse and dependence potential and harm associated with HCPs support rescheduling into schedu of the CSA.

iv. Balanced Presentation of the Eight-Factor Analysis

Nine commenters disagreed with the conclusions in the DEA's eight- factor analysis. These commenters asserted that the DEA's eight-factor analysis was not a balanced presentation and did not include the therapeutic benefits or the negative impact on patients with a legitimate medical use for HCPs. In addition, some of the commenters stated that the DEA's eight-factor analysis used flawed analytical methods and failed to show that HCPs were more dangerous or more abused than oxycodone. Several of these commenters requested that DEA include both sides of the clinical argument and peer-reviewed clinical research.

DEA response: The DEA reviewed the required eight factors in accordance with the provisions stated in **21 U.S.C. 811**(c), specifically exploring the abuse potential and potential harms of HCPs. The DEA's analysis also acknowledges that there is a currently accepted medical use, and accordingly therapeutic benefit, of HCPs. Consistent with the CSA, an evaluation of abuse and dependence potential, risk to the public health and safety, and other factors are included in the analysis. 21 U.S.C. 811(c). The CSA does not require that HCPs be more dangerous or abused than oxycodone in order to be placed in schedule II. Rather, relative abuse potential must be established. The DEA's analysis shows that HCPs have a high potential for abuse, and the abuse potential of HCPs is comparable to the schedule II controlled substance oxycodone. Thus, HCPs are appropriately placed in schedule II, along with oxycodone. Further, the analytical methods that were presented in the DEA's eight-factor analysis were consistent with the HHS's eight- factor analysis that was finalized in December 2013. The DEA used the best available methods based on current science to complete the eight- factor analysis.

2. Requirements Applicable to Prescriptions

a. Authority To Prescribe HCPs as Schedule II Controlled Substances

Nineteen commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns related to the restricted authority of mid-level practitioners to prescribe medications that are schedule II controlled substances.

DEA response: The DEA recognizes that some States do not allow all providers to prescribe schedule II controlled substances. However, it is outside of the DEA's scope of authority under the CSA to determine what categories of practitioners may prescribe controlled substances. Under the CSA, it is up to each State to decide who has the authority to prescribe controlled substances within that State. This is reflected in **21 U.S.C. 823**(f), which requires DEA to register a practitioner who is authorized under the laws of the State in which he practices unless the practitioner's registration would be inconsistent with the public interest. 21 U.S.C. 823, **824**. This is also echoed in **21 CFR 1306.03**, which states that a practitioner can issue a prescription for controlled substances so long as the practitioner is authorized to prescribe controlled substances by the jurisdiction where he is licensed to practice his profession and is registered or exempted from registration pursuant to **21 CFR 1301.22** (c) and **21 CFR 1301.23**. Each State has this authority, so long as it does not conflict with federal law.

b. Transmittal Method of HCPs as Schedule II Controlled Substances

i. Oral and Facsimile Prescriptions

Multiple commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns related to the transmittal methods available for schedule II as compared to schedule III controlled substances, specifically the circumstances required in order to provide oral prescriptions and to transmit prescriptions via facsimile. Both ultimate users and providers expressed concern that HCPs as schedule II controlled substances will not be available on nights and weekends. The were especially concerned about dental emergencies that might occur over the weekend. Four commenters stated that patients needing night or weekend prescriptions for HCPs will overburden Emergency Departments (EDs).

DEA response: The requirements for issuing an emergency oral prescription for a schedule II controlled substance do not hinder legitimate access to HCPs. The procedural requirements relating to transmission of a legitimate prescription do not hinder legitimate access either.

Contrary to concerns of commenters, practitioners will still be allowed to call-in prescriptions for HCPs in the event of an emergency. In the event of an emergency, as defined by 21 CFR 290.10, a pharmacist may dispense a schedule II controlled substance upon receiving oral authorization of a prescribing individual practitioner in accordance with **21 CFR 1306.11**(d).

ii. Triplicate Prescriptions

Five commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns regarding "triplicate prescriptions." One commenter stated that emergency physicians do not have triplicate prescription forms, and as a result, they will be required to prescribe drugs that are less effective for pain management. Two commenters stated that emergency physicians do not want to carry a triplicate prescription pad.

DEA response: Neither the CSA nor DEA regulations require prescriptions to be prepared in triplicate. The DEA recognizes that some States, such as Texas and California, require the use of triplicate prescription forms for some or all controlled substances. As stated in the November 19, 2007, final rule, "Issuance of Multiple Prescriptions for Schedule II Controlled Substances," the "DEA supports the efforts of States to take the specific action they deem necessary to prevent the diversion of controlled substances within their jurisdictions." 72 FR 64921, 64923.

> Under the CSA, Congress envisioned that the Federal and State Governments would work in tandem to regulate activities relating to controlled substances. This is reflected in **21 U.S.C. 903**, which indicates that Congress did not intend to preempt state controlled substance laws, so long as such state laws do not conflict with federal law. Thus, each state may enact controlled substance laws that go beyond the requirements of the CSA, provided such laws do not conflict with the CSA. Given this aspect of the CSA, it would not be appropriate for DEA to seek to preempt or supersede state laws relating to the prescribing of controlled substances, provided such laws do not conflict with the CSA or DEA regulations.

Id. at 64927.

c. Quantity and Frequency of Fills and Refills for HCPs as Schedule II Controlled Substances

Pharmacists, prescribers, and ultimate users expressed concern about the quantity and frequency of fills and refills for HCPs as schedule II controlled substances that would be allowed if HCPs were placed into schedule II.

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Several commenters, mostly ultimate users, asserted that up-scheduling would result in patients being limited to a 30-day supply of medication and would correspondingly need to begin seeing their doctors monthly. Other commenters, primarily pharmacists and physicians, expressed their belief that rescheduling HCPs will result in larger quantities of pills being authorized on each prescription to prevent patients from running out of medication and being in pain. Most of these commenters had corresponding concerns that these larger prescriptions would lead to more unused medication in the home that would be available for diversion. Examples include the following: One commenter mentioned his concern that since larger prescriptions would be authorized, he would be unable to monitor whether the patient is taking the medication or taking too much of it. An emergency physician opined that removing the ability to get refills on HCPs may result in prescriptions for more potent medications being issued. One ultimate user was concerned that the elimination of refills on HCPs would result in patients getting insufficient quantities to treat the acute illness for which it was prescribed.

DEA response: While courts have recognized that prescribing an "inordinately large quantity of controlled substances" can be evidence of a violation of the CSA,\12\ generally neither the CSA nor DEA regulations impose a specific quantitative minimum or maximum limit on the amount of medication that may be prescribed on a single prescription, or the duration of treatment intended with the prescribed controlled substance. The quantity prescribed and dispensed is limited in an emergency situation as defined by 21 CFR 290.10 when dispensing a schedule II controlled substance upon oral authorization in accordance with **21 CFR 1306.11**(d). The CSA and implementing regulations require all controlled substance prescriptions to be "valid." A prescription is not "valid" unless it is issued for a legitimate medical purpose and within the usual course of professional practice. **21 CFR 1306.04**(a). A pharmacist who fills a prescription has a corresponding responsibility, and the person who fills an illegitimate prescription is subject to penalty. Id.

\12\ United States v. Rosen, 582 F.2d 1032, 1036 (5th Cir. 1978).

While the CSA and DEA regulations generally contain no specific limit on the quantity that may be prescribed on a single prescription, or the duration of treatment intended for a single prescription, some States do impose specific limits on prescribing schedule II controlled substances. Likewise, some limitations on the quantity or frequency of schedule II controlled substances may be limited by individual prescription benefit providers. Any limitations imposed by State law apply, in addition to the corresponding requirements under Federal law, so long as the State requirements do not conflict with or contravene the Federal requirements. **21 U.S.C. 903**; **21 CFR 1306.12**(b)(1)(v); "Clarification of Existing Requirements Under the Controlled Substances Act for Prescribing Schedule II Controlled Substances," 70 FR 50408, Aug. 26, 2005.

Although the CSA prohibits refills of prescriptions for schedule II controlled substances, a practitioner may issue multiple schedule II prescriptions in order to provide up to a 90-day supply of medication in accordance with **21 CFR 1306.12**. Furthermore, DEA regulations do not require patients to be seen monthly by their provider. Rather, practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards how often to see their patients when prescribing controlled substances.

Note, however, that DEA regulations should not be "construed as mandating or encouraging individual practitioners to issue multiple prescriptions or to see their patients only once every 90 days when prescribing Schedule II controlled substances. Rather, individual practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards, whether it is appropriate to issue multiple prescriptions and how often to see their patients when doing so." **21 CFR 1306.12**(b)(2). The DEA does not regulate the general practice of medicine and the agency lacks the authority to issue guidelines (or make policy statements) that constitute advice on the general practice of medicine.

3. Patient Access to Medicine

The DEA received numerous comments, predominantly from ultimate users, who voiced concerns about the possible effects rescheduling would have on patients' access to appropriate treatment for pain. Commenters were concerned about the possible need for increased provider visits, and associated increased time and cost to receive medical care. Commenters were concerned about access to health care providers, such as possibly needing to change health care providers and in some cases having to drive longer distances to get to practitioners' offices because of limitations on types of practitioners who can prescribe schedule II controlled substances. Commenters were also concerned that rescheduling could result in doctors changing prescriptions to alternative medications which might be less effective for treating some kinds of pain and/or cause adverse health effects.

a. Impact on Prescribing Practices

Several commenters were concerned that because of the rescheduling, practitioners will be less likely to prescribe HCPs. One commenter suggested that since a practitioner can no longer call in or fax a prescription to the pharmacy, the practitioner will be reluctant to prescribe HCPs. Other commenters stated the scheduling action will impose additional burdens on practitioners and therefore they will stop prescribing for HCPs and prescribe less effective drugs. One commenter stated that many EDs do not typically prescribe schedule II narcotics. Likewise, two commenters suggested that cumbersome and slow ordering processes for schedule II substances will cause local shortages of HCPs, and thus practitioners will turn to prescribing other drugs.

DEA Response: The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination of whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, controlling HCPs as a schedule II controlled substance should not hinder legitimate access to the medicine. As recognized and noted by commenters, scheduling a medication does not make it impossible to prescribe, dispense, or administer the medication. However, it does alert prescribing- practitioners, pharmacists medical support professionals and perhaps even some patients and non-professional caregivers that the medication has potential dangers for addiction and misuse, and careful monitoring and evaluation of use of such drugs is necessary for appropriate patient care. "The placing of a drug into [a particular schedule of the CSA] will alert a physician that the drug does cause physical and psychological dependence. This is valuable information for a physician to possess before prescribing any drug." 50 FR 8104, 8107, Feb. 8, 1985 ("Schedules of Controlled Substances; Rescheduling of Buprenorphine From Schedule II to Schedule V of the Controlled Substances Act").

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The DEA does not intend for legitimate patients to go without adequate care. A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a). When a practitioner prescribes a medication that is a controlled substance for a patient, it must be because he/she has made a professional medical determination that it would be medically appropriate for the patient's medical condition to treat with that specific controlled substance.

The DEA recognizes that rescheduling a legitimately marketed pharmaceutical controlled substance may have some effect on the decision of a practitioner to prescribe that particular controlled substance. There may be some practitioners who are reluctant to prescribe a schedule II controlled substance although authorized by State law to do so. However, the DEA notes that other schedule II controlled substances are widely prescribed. Given that classification has not deterred practitioners from prescribing those drugs, the DEA believes that when a practitioner makes a medical determination that a particular controlled substance is appropriate to treat a patient's medical condition, the practitioner will prescribe the appropriate controlled substance, regardless of the substance's schedule. The DEA notes that a doctor from New York, one of the States that has already scheduled HCPs as schedule II controlled substances under State law, asserted in his comment that up-scheduling "has reduced unconscious (or conscience-less) prescribing without impacting patients' access to medications."

b. Impact of Criminal Action

Some commenters expressed concern that transferring HCPs to schedule II would deter prescribers from properly treating pain for fear of facing criminal action. According to one commenter, many providers limit the number of pills for schedule II medications "because they feel they are being watched by monitoring programs and are afraid the DEA 'will investigate' them for too many CII scripts."

DEA response: One of the most important principles underlying the CSA is that every prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a); U.S. v. Moore, 423 U.S. 122 (1975) (holding registered physicians may be prosecuted for violation of the CSA when their activities fall outside the usual course of professional practice). The DEA policy statement entitled "Dispensing Controlled Substances for the Treatment of Pain," 71 FR 52715, Sept. 6, 2006, makes clear that this longstanding requirement should in no way interfere with the legitimate practice of medicine or cause any practitioner to be reluctant to provide legitimate pain treatment. Practitioners (as well as ultimate users) become subject to administrative, civil, and/or criminal action when their activity involving controlled substances is not authorized by, or is in violation of, the CSA, regardless of whether the activity involves a schedule II controlled substance or a schedule III controlled substance.

c. Impact on Drug Availability

Two commenters suggested this rule will result in limited drug availability because wholesalers are limiting distributions to community pharmacies. These commenters assert that if a pharmacy goes over a pre-determined amount, they cannot obtain the needed pharmaceuticals until the following month. The commenter asserted that this practice may have particularly adverse impacts in rural areas where a pharmacy may only be serviced by one distributor. Another commenter suggested there will be local shortages of HCPs because of the cumbersome and slow schedule II ordering process. Two commenters were concerned that limited availability may result from delays associated with manufacturer production due to annual production requirements for schedule II controlled substances.

DEA response: DEA registered distributors are required to provide effective controls against diversion of controlled substances. However, the DEA does not limit the quantity of controlled substances that may be legitimately distributed to pharmacies. Any arbitrary limits placed on community pharmacies by distributors are the result of a business decision of that distributor.

The DEA does impose requirements for distributors to operate a system to disclose suspicious orders of controlled substances. **21 CFR 1301.74**(b). Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency. Id. Part of the due diligence associated with that requirement, as well as the general requirement under **21 CFR 1301.71**(a) for registrants to "provide effective controls and procedures to guard against theft and diversion of controlled substances," is to "know your customer." While order volume may be one indicator of a suspicious order, the totality of circumstances must be used in making a determination. Generally, no single indicator is independently a suggestion that a given order is suspicious. Order volume should be examined not only on an industry-wide comparison level, but also on a local level. For example, a pharmacy located near an oncology clinic may be more likely to regularly order higher volumes of certain controlled pharmaceuticals than one that is not.

The DEA does not find evidence to support the claim that the ordering process for schedule II controlled substances will result in limited availability of HCPs. A DEA Form 222, or its electronic equivalent--the Controlled Substance Ordering System (CSOS), is required for all distributions of schedule I or II controlled substances, with specific exceptions, **21 U.S.C. 828**(a); **21 CFR 1305.03**, which enables the DEA to monitor the flow of these controlled substances from their point of manufacture through commercial distribution. It takes approximately an hour to complete each order using the paper DEA Form 222. It takes approximately three minutes to complete an order using CSOS. (The DEA Form 222 permits ten line items per form; electronic orders are not subject to the same requirement and may contain an unlimited number of transactions (line items)). While CSOS transactions are faster, the paper DEA Form 222 orders are also able to be processed quickly through the system. In 2013, 109,632 registrants ordered schedule I or II controlled substances. About 4.8 million orders were processed on Form 222s and 924,3[illegible] were processed electronically via CSOS (approximately 16% of all orders). The paper orders represented roughly 27.7 million transactions (or about 6 per order) electronic orders represented roughly 21.2 million transactions or slightly more than 23 per order.

There should be no impact on availability due to schedule II annual production requirements (i.e., manufacturing quota). Registrants that manufacture hydrocodone are already required to obtain an annual quota in order to manufacture hydrocodone because it is a schedule II controlled substance unless and until it is formulated into dosage form HCPs.

Manufacturing quotas are issued to bulk manufacturers who manufacture either from synthetic routes (e.g., hydrocodone from codeine), or extraction from narcotic raw material.

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Bulk manufacturing quota will not be impacted by the movement of HCPs from schedule III into schedule II.

Procurement quotas are typically issued to dosage form manufacturers and repackagers or relablers for manufacturing activities. As related to HCPs, a procurement quota is required to: (1) Receive bulk Active Pharmaceutical Ingredients to be manufactured into dosage units; and (2) for a company to receive bulk finished dosage units for relabeling or repackaging.

d. Providers Authorized To Prescribe Schedule II Controlled Substances

Nine commenters expressed concern about the ability to access health care providers who can prescribe schedule II controlled substances. Specifically, commenters stated that mid-level health care providers such as physician assistants and nurse practitioners, who provide primary health care, cannot prescribe schedule II controlled substances in many States. As a result, these patients will not have access to the medicine they need to treat their pain. In addition, one commenter stated this will have a negative impact on patients who visit rural practices where mid-level practitioners often prescribe pain medication. Moreover, one commenter stated the scheduling action would make it mandatory for a patient to see a physician for pain. Another commenter stated that because of this scheduling they would now have to find new doctors, which would increase travel time and the amount of money spent on gas.

DEA response: State authorization to handle controlled substances is both a necessary precondition for Federal authorization to handle controlled substances and a qualifying determinate as to the extent of the practitioner's scope of authority in regard to such substances. U.S. v. Moore, 423 U.S. 122, 141 (1975) ("The federal registration, which follows automatically, extends no further [than the scope of authority granted by the State to practice medicine and to dispense drugs in connection with their professional practice]."). A DEA registered practitioner may only engage in those activities involving controlled substances that are authorized by the laws of the State on which the practitioner's Federal registration is based. If an individual practitioner, or a class of practitioners, has not been granted authorization to prescribe certain controlled substances that is the rightful determination of the State under its authority to regulate the practice of medicine.

e. Treatment for Pain

Concerns were raised that changes in the scheduling for HCPs could drive the use of alternative treatments. One class of commenters who were particularly concerned about this was emergency physicians who work in States that require triplicate prescriptions and/or facilities whose policy is not to handle schedule II controlled substances in their emergency departments. Some emergency providers in triplicate- prescription States said that they did not carry triplicate prescriptions due to concerns about them being stolen. Some emergency physicians who work in States that require triplicate prescription forms (but who are able to write schedule II controlled substance prescriptions while working in their emergency departments) stated that if "forced to get a triplicate," then he will start writing for more schedule II controlled substances, such as Percocet, because it is a "better pain med[icine] than HCPs." Other commenters were concerned that some prescribers might switch to prescribing "stronger drugs with significant abuse potential," or alternatively switch to medications such as non-steroidal anti-inflammatory drugs (NSAIDs) which are less effective for treating some kinds of pain and may cause other adverse effects, leaving people in untreated pain. One commenter was concerned that tramadol would be prescribed in place of HCPs, which worried them because of issues with tramadol specific to renal patients.

DEA response: The DEA does not regulate the general practice of medicine and the agency lacks authority to issue guidelines (or make policy statements) that constitute advice on the general practice of medicine. A prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a); U.S. v. Moore, 423 U.S. 122 (1975). A practitioner must use sound medical judgment to determine which controlled substance they will prescribe to appropriately treat his or her patient's medical condition, rather than make a determination based upon whether a triplicate prescription form is required by the State or by their employer's policy to not prescribe schedule II controlled substances.

f. Shift to the Black Market

Several commenters stated that making HCPs schedule II controlled substances would limit access to HCPs, causing people to buy drugs on the street, including HCPs and heroin.

DEA response: As discussed above, schedule II controlled substances are readily available for legitimate medical use.

g. Monitoring Access

A national advocacy group for cancer patients requested that the DEA "require monitoring plans and an annual report to Congress, in the event that HCPs are upscheduled, that assess the impact on access by patients with legitimate needs, as emphasized and urged by HHS" and to "adjust policy accordingly if it finds that access is impeded for patients who legitimately need HCPs for pain management."

DEA response: Once upscheduled the DEA will continue to monitor the diversion of HCPs. However, it is outside the scope of the DEA's authority under the CSA to require monitoring plans or reports not authorized under the Act.

4. Impacts on Unique Populations

The DEA received several comments regarding the impact on patients who suffer from chronic pain, cancer, rare diseases, chronic and end- stage renal disease, as well as dental and surgical post-op patients, and rural residents. Many commenters also voiced concerns about possible effects of rescheduling on the elderly and disabled. Several commenters who are affected by chronic pain voiced a concern that the scheduling action will be a burden and make it harder for them to obtain their medicine. As a result, these commenters stated they will suffer solely because of the people that abuse HCPs. Another commenter stated that because of this burden, patients might start self- medicating. One commenter said that practitioners will start prescribing drugs that are not as effective as HCPs, which could have a negative impact on patients mentally. One commenter stated that many cancer patients are in chronic pain, and because of this action, these patients will suffer as they cannot get their required medication. Others suggested post-op patients will have to suffer in pain after their surgeries because they will not be able to get the required medications from doctors on weekends. Several commenters stated that patients in rural areas who are currently seen by mid-level practitioners will need to drive an hour or more to be treated by a physician because their mid-level provider is not authorized to issue prescriptions for schedule II controlled substances. In addition, another commenter stated that many rural physicians are already

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overbooked, which will cause rural patients to suffer in pain until they can get an appointment. Another commenter stated that rural patients have a tough time physically picking up handwritten prescriptions. Several commenters noted that the nearest doctor is more than an hour away and that having to drive that distance once a month to obtain HCPs is inconvenient.

DEA response: Scheduling determinations are based on scientific determinations regarding the substance's potential for abuse, its potential for psychological and physical dependence, and whether the substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based merely on the population it is intended or approved to treat.

5. Impact on Long-Term Care Facilities (LTCFs)

a. Treatment for Pain

Many commenters, including two U.S. Senators, requested that the DEA closely examine possible impacts of rescheduling HCPs in the long- term care facility (LTCF) setting. Many commenters had concerns that placing HCPs into schedule II will impact a substantial number of LTCF residents and may result in untreated pain due to the lack of ready- access to other appropriate medications. For example, according to one commenter, "HCPs are the current, albeit less preferred alternative because of its combination with acetaminophen, which has to be restricted in older adults due to toxicity risk. However, long-term care providers have been forced to use HCPs as a substitute for Schedule II drugs" because they are more readily available for administration due to less restrictive handling requirements for controlled substances in lower schedules than schedule II. According to this same commenter, "the remaining pain care options still in schedule II are not as clinically effective in treating pain for the elderly as HCPs."

Two commenters stated that LTCF residents, especially post-surgical patients, need medications immediately and that obtaining prescriptions is not quick because most LTCFs do not operate with in-house doctors on site.

DEA response: As previously discussed, scheduling determinations are based on scientific determinations regarding the substance's potential for abuse, its potential for psychological and physical dependence, and whether the substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). Nonetheless, the DEA has promulgated many regulations to accommodate the unique circumstances of LTCF residents. For example, in accordance with **21 CFR 1306.11**(f), a prescription for a schedule II controlled substance for a resident of an LTCF may be transmitted by the practitioner or practitioner's agent to the dispensing pharmacy by facsimile. In accordance with **21 CFR 1306.13**(b), a prescription for a schedule II controlled substance written for a patient in an LTCF may be filled by the pharmacy in partial quantities to include individual dosage units.

b. Request for Exemption for LTCFs

Several commenters requested that the DEA waive/exempt LTCFs from the more restrictive schedule II handling requirements with respect to HCPs. Some commenters asserted that such a waiver/exemption would be justified based on their assertion that there is a lower risk of misuse, abuse, and diversion of HCPs in an LTCF setting as compared to other settings. One nationwide professional association stated that:

[T]he long-term care setting has special and unique protections against diversion that are required by federal regulations and makes abuse and diversion very difficult and therefore, less likely to occur. * * * The regulatory standards and mandatory procedural checks in most cases make it difficult or impossible for any suspected abuse or diversion to occur over a sustained period of time. This makes diversion by staff difficult * * *. Other than anecdotal case here and there, there is no evidence that diversion is a systemic or frequent problem in SNF [skilled nursing facility] setting nor that the current proposed rule will correct [it].

This same commenter asserted that the "nursing home population is unlikely to be drug abusers" because "[t]heir health conditions often make them bed-bound or otherwise dependent on nurses for the administration of their medications."

DEA response. Nursing home residents take, on average, eight to ten medications per day.\13\ At least 17% of those medications are unused.\14\ Controlled substance medications are often stored and administered in LTCF settings as monthly punch cards (a.k.a. "bingo cards"), and liquid controlled substances are often dispensed in large-volume packaging.\15\ \16\ In addition, a 2011 report by the HHS Office of Inspector General found that almost all sampled nursing facilities employed one or more individuals with at least one criminal conviction, and nearly half of sampled nursing facilities employed five or more individuals with at least one conviction. Further, 44% of employees with convictions were convicted of crimes against property (e.g., burglary, shoplifting, writing bad checks).\17\ LTCFs are unique potential sources of diversion because the care provided to residents results in the accumulation of large amounts of controlled substances in a single, un-registered, relatively unsecure environment, where the disabled and elderly cannot defend themselves or adequately report what has happened.

\13\ The Lewin Group. CMS Review of Current Standards of Practice for Long-Term Care Pharmacy Services: Long-Term Care Pharmacy Primer. Prepared for: Centers for Medicare and Medicaid Services. December 30, 2004.

\14\ Gary Bazalo, MS, MBA, and Richard C. Weiss, MS, Managed Solutions, LLC. Measurement of Unused Prescription Drugs in Medicare Part D Nursing Stays. Jan. 12, 2011 at p. 6 (reporting survey results of consulting pharmacists conducted by the American Society of Consultant Pharmacists).

\15\ Marti A. Burton and Linda J. May Ludwig, Fundamentals of Nursing Care: Concepts, Connections & Skills 857 (2011); Norman V. Carroll, Ph.D., Michael T. Rupp, Ph.D., and David A. Holdford, Ph.D., Analysis of Costs to Dispense Prescriptions in Independently Owned, Closed-Door Long-Term Care Pharmacies, 20(3) JMCP 291 (2014) (76% of independently owned, closed-door pharmacies dispense 76% of doses to LTCFs in 28-31 day cycles).

\16\ Comment of American Society of Consultant Pharmacists on Docket No. DEA-316, "Disposal of Controlled Substances," Feb. 19, 2013 available at http://www.regulations.gov/#!documentDetail;D=DEA- 2012-0008-0144.

\17\ U.S. Department of Health and Human Services, Office of Inspector General, OEI-07-09-00110, Nursing Facilities' Employment of Individuals with Criminal Convictions (2011), available at http://oig.hhs.gov/oei/reports/oei-07-09-00110.pdf.

While focusing on the limited mobility of many residents in LTCFs as justification for why LTCFs should be able to adhere to less restrictive handling requirements for HCPs, commenters gave little consideration to potential diversion by employees, contractors, outside professionals, or visitors who may have access to their facilities. Direct access to controlled substances around a vulnerable population provides many opportunities for diversion of controlled substances, to the detriment of the LTCF

residents as well as the general public. For example, the Oregon Aging and People with Disabilities Division, alone, investigated 29 instances of drug theft at 17 different LTCFs in three counties, between 2009 and 2013.\18\ The average was 15.8 cases of medication theft per 1,000 beds/units, with the most often stolen products being narcotic

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painkillers--such as HCPs.\19\ These medication thefts occurred in both large nursing homes and small adult foster homes.\20\

\18\ Mac McLean, Drug Theft Affects Care, The Bulletin, Sept. 8, 2013, available at http://www.bendbulletin.com/news/1340250-153/drug-theft-affects-care.

\19\ Id.

\20\ Id.

Although not addressing LTCFs directly, the Mayo Clinic has reported on the diversion of drugs from within health care facilities and the threat to public health and safety such actions cause.\21\ Those risks included risk to patients receiving adulterated or contaminated drugs in place of the diverted drug as well as the risk of receiving substandard care from addicted employees.\22\ The Oregon investigations also included reports of having a patient's medication replaced with blood pressure medication--thus causing the combined risk of not receiving proper medication with the risk of overdose of another medication.

\21\ Keith H. Berge, et. al., Diversion of Drugs Within Health Care Facilities, a Multiple-Victim Crime: Patterns of Diversion, Scope, Consequences, Detection, and Prevention, 87(7) Mayo Clin. Proc. 674 (2012).

\22\ Id.

The most cursory of searches readily reveals multiple allegations reported in the news of thefts of controlled substances in nursing homes. For example, in 2012 six nursing home employees in Oklahoma were charged with operating a drug ring out of the facility for whom they were employed. Charges Filed in Nursing Home Drug Theft, KWGS News, July 5, 2012, available at http://publicradiotulsa.org/post/charges-filed-nursing-home-drug-theft. The Oklahoma Bureau of Narcotics (OBN) reported that 9,000 dosage units of controlled substances had been diverted from the facility by the nursing home employees, 8,400 of which involved hydrocodone. Press Release, Oklahoma Bureau of Narcotics and Dangerous Drugs Control (July 5, 2012) (on file with the Oklahoma Bureau of Narcotics); Oklahoma Nursing Home Employees Accused of Running Drug Ring: State v. Alexander, 15 No. 1 Westlaw Journal Nursing Home 4 (2012). The spokesman for OBN stated that employees would call in fraudulent prescriptions of hydrocodone for residents: "These residents had not been prescribed the Hydrocodone by doctors. There is no evidence that any resident was deprived of their legitimate medications. Evidence suggests some of the employees would personally use small amount of the diverted medication, but the majority of the fraudulent drugs were sold on the streets * * *." Id.

Criminal acts at LTCFs "often go undocumented, are seldom reported to law enforcement, and are rarely prosecuted."\23\ Even so, theft and diversion at LTCFs likely occurs on a local level, and when reported, are investigated and prosecuted at the local level. The diversion of controlled substances at LTCFs, whether wide-spread or discrete events, are a threat to the public health and safety, especially considering that such activity poses a real and direct threat to a vulnerable population. Public health and safety threats to disadvantaged, underrepresented, and historically vulnerable populations, including the elderly and mentally, physically, and emotionally/behaviorally disabled, disordered, or challenged, must be taken that much more seriously by those public bodies charged with protecting the public health and welfare. The DEA further notes that the misuse, abuse, and diversion of controlled substances, including pharmaceutical controlled substances, are not limited to any particular age group or functional level.

\23\ Wes Bledsoe, Criminal Offenders Residing in Long-Term Care Facilities, 2(3) J Forensic Nurs. 142 (2006).

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c. Transmission Method for Prescriptions

One commenter requested two changes to the transmittal methods for prescriptions: (1) Allow a prescribing practitioner to call in to the pharmacy an order for a limited supply, up to a 72 hour quantity, of a schedule II medication for an LTCF patient in an emergency situation, under existing regulations for schedule III-V controlled substances; and (2) Allow a practitioner's agent, acting on behalf of a prescribing practitioner, to call in the prescribing practitioner's verbal order for a small (72 hour) supply of a schedule II medication for an LTCF patient in an emergency situation, under existing regulations for schedule III-V controlled substances.

DEA response: The CSA requires that prescriptions for schedule II controlled substances be written, except in emergency situations as defined by the HHS. **21 U.S.C. 829**(a). Pursuant to **21 CFR 1306.11**(d), in the case of an emergency situation, a pharmacist may dispense a schedule II controlled substance upon receiving oral authorization from a prescribing individual practitioner provided that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period (dispensing beyond the emergency period must be pursuant to a written prescription signed by the prescribing individual practitioner).

The DEA recognizes the unique challenges and issues pertaining to handling and using controlled substances at LTCFs and has previously addressed these issues within the limits of the CSA.\24\ For example, a prescription for a schedule II controlled substance for an LTCF resident may be transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile. **21 CFR 1306.11**(f). In addition, a prescription for a schedule II controlled substance for an LTCF resident may be filled in partial quantities to include individual dosage units. **21 CFR 1306.13**(b).

\24\ E.g., "Preventing the Accumulation of Surplus Controlled Substances at Long Term Care Facilities," 66 FR 20833, Apr. 25, 2001; "Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies," 75 FR 61613, Oct. 6, 2010.

It is emphasized that a DEA registered practitioner may not delegate to a nurse, a pharmacist, or anyone else, his or her authority to make a medical determination whether to prescribe a particular controlled substance. Note that the practitioner remains responsible for ensuring that the prescription conforms in all essential respects to the law and regulations, **21 CFR 1306.05**(f). 75 FR 61613, 61614, Oct. 6, 2010. This requires the practitioner alone to determine on a prescription by prescription basis whether the prescription is supported by a legitimate medical purpose and that all the essential elements of the prescriptions are met.

d. E-Prescribing

One commenter requested that the DEA "promote the adoption of e- prescribing by requiring facilities and their respective pharmacy suppliers to allow physicians to electronically prescribe controlled substances consistent with the law and appropriate safeguards."

DEA response: This request is outside the scope of this rulemaking.

e. Emergency Kits

One commenter requested that the DEA "promote adoption of consistent and effective laws and policies across all states for the content and use of emergency kits (E-Kits) in the PA/LTC setting."

DEA response: This request is outside the scope of this rulemaking.

6. Abuse Prevention

Commenters raised concerns that, despite the scheduling of drugs, individuals will always find substances to abuse. These commenters argued that the proposed schedule II controls for

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HCPs will not address or stop the abuse of HCPs because other schedule II controlled substances such as oxycodone products are highly abused and diverted.

DEA response: The cycle of abuse between licit and illicit opioids, abuse of licit and illicit non-narcotic prescription drugs, and continued abuse of schedule I controlled substances such as LSD demonstrates that what individuals and communities are facing is not a problem specific to HCPs. Rather, it is an addiction problem. Heroin use and prescription drug abuse are both addictions that begin with use and are sustained and promoted through increased trafficking. This serious public health problem can be addressed by education, appropriate screening and treatment, recovery, support, and enforcement. These initiatives can be effective regardless of whether the problem is fed by heroin or prescription drugs, including HCPs, and the DEA supports all of these initiatives to address both prescription drug misuse and abuse and heroin use.

[redacted]The problem of prescription drug abuse is fueled due to a combination of excessive prescribing, drug availability through friends and family, rogue pain clinics, practitioners who prescribe pharmaceutical controlled substances without legitimate medical purpose or outside the usual course of professional practice, pharmacies that dispense illegitimate prescriptions, and supply chain wholesalers and manufacturers that fail to provide effective controls and procedures to guard against diversion--all of which fuel illicit access at the expense of the public health and safety.

A balanced drug control strategy, one that includes strong enforcement, education, prevention, and treatment components, can make significant progress in protecting our nation from the dangers of drug abuse.

The DEA's enforcement responsibility as it pertains to drugs and other substances is clearly delineated in Federal law. Pursuant to **21 U.S.C. 811**(a), the CSA authorizes the DEA, under authority delegated by the Attorney General, to add to a schedule any drug or other substance if it is found that the drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by **21 U.S.C. 812**(b). As such, the legal system established by Congress specifically accounts for new substances to be added to the list of controlled substances without regard to the number of substances already controlled. See also 21 U.S.C. 812(a) ("Such schedules shall initially consist of * * *" (emphasis added)).

The dynamic structure constructed in the establishment of the schedules of controlled substances takes into consideration that the conclusions reached under each of the eight-factors specified under **21 U.S.C. 811**(c) may change over time. Scientific knowledge about a drug or substance grows, pharmacological knowledge increases, history and current patterns of abuse change, etc. The CSA scheduling protocols also take into account that new drug applications for drugs with abuse potential are submitted to and approved by the FDA as well as that clandestine chemists attempt to manipulate the molecular structures of controlled substances to create synthetic drugs that would have the same pharmacologic properties of a controlled drug, but not expose the chemist or distributor to criminal violations. The CSA, however does not only account for one-time scheduling determinations regarding the control of drugs and other substances. In addition to the initial control of drugs and other substances to schedules, the CSA likewise takes into account and provides for the transfer of a drug or other substance between schedules, or for a drug or other substance to be removed entirely from the schedules. 21 U.S.C. 811(a) and (b).

Nevertheless, the DEA disagrees that control of HCPs in schedule II will not decrease abuse of HCPs. Control of HCPs in schedule II will result in increased monitoring of these drugs as well as increased safeguards for legitimate prescriptions.

7. Diversion Prevention

Commenters also questioned whether moving HCPs to schedule II would reduce diversion of HCPs. These commenters argued that the proposed schedule II controls for HCPs will not address or stop the diversion of HCPs because other schedule II controlled substances such as oxycodone products are still diverted despite their schedule II status.

DEA response: The DEA disagrees that control of HCPs as schedule II controlled substances will not decrease their diversion. Control of HCPs into schedule II will result in increased monitoring of these drugs as well as increased safeguards for legitimate prescriptions.

8. Responsibilities of Pharmacists

The DEA received many comments, from pharmacists, physicians, ultimate users, and the general public, who were concerned that the increased administrative burden on pharmacists that might occur as a result of moving HCPs into schedule II would cause pharmacists to devote time to the administrative burdens rather than on patient counseling and safety. Commenters stated that the administrative burden would be greatly increased in the pharmacy setting because: separate prescriptions would have to be entered for every HCP; pharmacists would have to count the prescriptions, as technicians are not legally allowed to do so in some States; inventories would be required of all HCPs; and increased workload associated with recordkeeping requirements (i.e., DEA Form 222).

[redacted]*EA response:* The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination of whether a substance hould be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**.

9. Requirements Applicable to Manufacturers and Distributors

a. Effective Date

Several of the comments submitted by members of industry (manufacturers, wholesale distributors, veterinary distributors, retail pharmacies), and/or trade associations representing them, focused on the timeframe for implementation of various handling requirements. A national trade association comprised of manufacturers and distributors of generic pharmaceutical products requested that the DEA "allow sufficient time for all parts of the supply chain to integrate the new requirements into their business operations." Similar requests were also posed by an individual manufacturer of HCPs, a wholesale distributor, and a retail pharmacy/mail pharmacy service provider, each who proposed a blanket six month delay before a final rule would go into effect. A national trade association comprised of distributors requested that the DEA allow at least 12 to 24 months, with opportunity for additional extension for individual registrants on an as needed basis, from the effective date of the final rule to allow for changes to facilities, policies and procedures. The national trade association requested that during the interim period registrants be allowed to continue to hold HCPs in cages rather than to be immediately required to place these items in vaults. Specifically, the association proposed that the DEA "[r]ecognize a registrant's compliance with the physical security requirements if the registrant has, by the implementation date of the storage

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requirements resulting from a rescheduling decision, submitted to the agency plans, blueprints, sketches, or other materials, including but not limited to signed contracts with contractors to implement any proposed physical security changes to the registrant's premises, and has otherwise been and continues to be in compliance with physical security requirements pursuant to [**21 CFR 1301.72**] for HCPs subject to this rescheduling decision as of the date prior to the effective date of a rescheduling decision." The national trade association additionally requested that the DEA provide specifics regarding the "process for submission of the materials demonstrating the vault construction plans" and how they might be able to "demonstrate compliance in lieu of vault construction completion."

DEA Response: In accordance with the Administrative Procedure Act, generally, DEA scheduling actions are effective 30 days from the date of publication of the final rule in the Federal Register. 5 U.S.C. 553(d). In order to ensure the continued availability of HCPs for legitimate medical use, while also ensuring they are not subject to misuse, abuse, and diversion, the DEA is establishing an effective date 45 days from the date of publication of this final rule. This 45-day period is a reasonable amount of time for registrants to comply with the handling requirements for a schedule II controlled substance and was established upon a full consideration of the totality of circumstances specific to HCPs.

The DEA understands that 45 days to implement all schedule II handling requirements may be perceived as short by some distributors. While the DEA acknowledges that the supply chain will need to plan and coordinate efforts, and may even need to temporarily modify existing ordering and inventory management practices, the DEA is required to consider the risk of diversion and risk to public health and safety of U.S. residents.

As summarized in the NPRM and the DEA presentation at the January 24, 2013, public DSaRM meeting, available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagmentadvisorycommittee/ucm346941.pdf, and discussed in detail in the supporting eight-factor analyses, HCPs are being abused with adverse effects both individually and to the public health and safety, accordingly, it should be placed into schedule II as soon as practicable. Prescription drug abuse refers to the intentional misuse of a medication by using more than medically indicated in order to feel the drug's psychoactive effects and/or using the drug in a manner that is not medically indicated. Prescription drug abuse has [redacted]creased exponentially in the last 15 years and is the Nation's fastest growing drug problem. Factors including excessive prescriptions, drug availability through [redacted]ends and family, Internet trafficking, rogue pain clinics, pharmacies that dispense illegitimate prescriptions, and failed safeguards by wholesalers and manufacturers [redacted]o guard against diversion have all contributed to the prescription drug abuse problem.

[redacted]The increase in prescription drug abuse has also been attributed to ease of obtaining the drug and the misconception that abusing prescription drugs is much safer than using and abusing street drugs. According to the 2012 Partnership Attitude Tracking Study (PATS), 43% of teenagers believe that prescription medications are "easier to obtain" than illegal drugs. In addition, the 2012 PATS also reported that 27% of teens believe that misusing or abusing prescription drugs is "safer" than using street drugs. Some of the increased demand for prescription opioid painkillers is from people who use them non- medically (using drugs without a prescription or just for the high they cause), sell them, or get them from multiple prescribers at the same time (CDC Vital Signs, July 2014, Opioid Painkiller Prescribing, Where You Live Makes a Difference).

According to the 2012 National Survey on Drug Use and Health (NSDUH), approximately 2.6% or 6.8 million people ages 12 and older are nonmedical users of prescription drugs. Abuse of opioid drugs, including HCPs, can lead to addiction, respiratory depression, and death. There were more than 16,000 deaths due to abuse of opioid drugs including HCPs in 2010. That is more than 1,333 people dying each month. According to the CDC, 38,329 people died from a drug overdose in the United States in 2010. Of these deaths, 22,134 people or 60% involved prescription drugs. Seventy-five percent of the prescription drug overdose deaths (16,651 people) were due to opioid drugs primarily containing oxycodone, hydrocodone, or methadone.

Abuse of prescription drugs is particularly alarming since data are strongly indicating that prescription opioid drug abuse can lead to heroin abuse.\25\ Specifically, data show that the population with the highest rate of heroin initiation was that population with prior nonmedical pain reliever use. The rate of heroin initiation among prior nonmedical pain reliever users was approximately 19 times greater than those who did not have such prior use. The rate of heroin initiation increased with increases in the frequency of past year nonmedical pain reliever use. Id.

\25\ SAMHSA, Center for Behavioral Health Statistics and Quality, Data Review, Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. August 2013 available at http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm.

The DEA has long held that increased heroin use is driven primarily by an increase in the misuse and abuse of prescription opioid drugs, particularly HCPs. The DEA's investigations indicate that the cost of prescription opioid drugs on the street may be as high as $80.00 per tablet and makes it difficult for teens and young adults to purchase drugs in support of their addiction. Therefore, abusers of prescription opioid drugs may resort to using heroin, a much cheaper alternative that produces similar euphoric effects, to keep the drug seeker/abuser from experiencing painful withdrawal symptoms. According to the most recent NSDUH, there were 335,000 heroin users in 2012, which is more than double the number in 2007 (161,000). In the decade from 2002 to 2011, the annual number of drug poisoning deaths involving heroin doubled, from 2,089 deaths in 2002 to 4,397 deaths in 2011.\26\

\26\ Hedegaard H, Chen L-H, and Warner M. Quick Stats: Rates of Drug Poisoning Deaths Involving Heroin, * by Selected Age and Racial/Ethnic Groups--United States, 2002 and 2011, MMWR 2014; 63:595.

HCPs are the most prescribed drug in the United States. Production of HCPs has increased from 15,359 kilograms in 1998 to 63,338 kilograms in 2012 (IMS, 2014). Increased production of HCPs is directly due to the increased prescription of these drugs to treat and alleviate pain. Even though there is legitimate use of HCPs, data indicate that a considerable population misuse HCPs. The National Poison Data System (NPDS) reported during the period of 2006-2012, that 45.4% of the total exposures to HCPs were considered intentional exposures, a surrogate to usage for abuse or misuse. The high percentage of HCPs for misuse supports that HCPs are contributing to prescription opioid drug abuse and may consequently lead to heroin abuse and death.

In order to prevent continued misuse, abuse and diversion, it is necessary to set an effective date for this scheduling action, including security and labeling requirements, with all reasonable haste.

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After careful consideration of the risk to the U.S. public health and safety related to the diversion and abuse of HCPs, the DEA believes the 45-day effective date is reasonable.

From the 2007 Economic Census, the DEA estimates that the inventory turnover ratio for the industry \27\ is approximately 11.3.\28\ The inventory turnover ratio represents the number of times the inventory sells (turns) in a year. The 11.3 inventory turnover ratio equates to an average of 32 days to sell inventory. The 11.3 turnover ratio is consistent with that of large distributors where financial information was publicly available and reviewed. The inventory turnover ratio is a reasonable estimate for the entire industry and all products under the circumstances. Publicly reviewed data show that about 85% of all revenues (an indirect indicator of dosage units moved) from drug distribution in the United States come from three public wholesalers, each with annual revenue in the billions. The DEA additionally notes that many regional and specialist pharmaceutical wholesalers have been acquired by the largest three distribution companies. Because the 32 days to sell inventory is an average based on industry-wide Census data, it is possible for an individual company and/or product line to experience a shorter or longer time to sell.

\27\ NAICS 424210--Drugs and druggists' sundries merchant wholesalers; Merchant wholesalers, except manufacturers' sales branches and offices.

\28\ The inventory turnover ratio of 11.3 was calculated by dividing the 2007 "cost of goods sold" for the industry of $280,481,051,000 by the average end-of-year 2006 and 2007 total inventories of $24,782,835,000.

Since HCPs are the most prescribed opioid drugs in the United States, with over 137 million prescriptions dispensed in 2013,\29\ the DEA expects distributors to continue to receive and distribute HCPs at high volume and with regularity; thus, anticipating shorter than average days to sell HCPs than the overall industry average ratio. In other words, the very high volume of sales indicates that HCPs are moving very quickly through the supply chain to meet demand, indicating high turnover and low inventory. However, to accommodate those manufacturers and distributors that have lower than average industry turnover ratio, the DEA is establishing an effective date of this final rule, including labeling and packaging requirements, 45 days from the date of publication. Based on the available information, and the lack of specific information regarding manufacturer and distributor inventory practices with respect to HCPs, the DEA believes this will provide a reasonable time for distributors to sell existing stock with pre-control labeling and packaging (C-III) and to stock inventory with post-control labeling and packaging (C-II).

\29\ IMS Health, National Sales Perspective TM (NSP).

The DEA anticipates manufacturers to begin developing inventory of HCPs with schedule II labels prior to the effective date of the rule to have stock ready to be distributed upon effect of this rule. The DEA estimates that 45 days is a reasonable amount of time for manufacturers and distributors to deplete existing inventory of HCPs. The packaging and labeling requirements for manufacturers and distributors do not apply to dispensers. Dispensers with HCPs in commercial containers labeled as schedule III may continue to dispense these HCPs after the implementation of this rule.

The DEA believes that HCPs labeled as C-III can be exchanged with HCPs containing new labels at nominal cost. The rule allows this exchange in a similar manner to the return of expired controlled substances authorized under existing regulations. Since manufacturers are expected to have ready-inventory of HCPs with new labels, exchanges are expected to occur without delay. In this rule, the DEA is allowing transfers of HCPs labeled as schedule III to be returned in exchange for HCPs labeled as schedule II without the requirement for procurement quota. Therefore, the DEA believes HCP manufacturers and distributors can reasonably make the necessary labeling changes and have inventory to meet the demands of customers.

The DEA acknowledges distributors may need to make some modifications to their inventory management system and operating procedures. However, these changes are expected to be procedural changes with only nominal impact on the burden created by the activities. For example, a distributor will need to receive, unpack, record the product in inventory, store, accept orders, and ship out to customers. These are all activities that occur regardless of the control status of HCPs. The anticipated changes may be a modification to the inventory management system and possible expansion of storage space (vaults).

The DEA has carefully considered the security requirements for compliance with this rule. As confirmed by the national trade association comprised of distributors, current distributors of HCPs are DEA registrants with existing controlled substance storage facilities that comply with DEA regulations. The DEA believes the DEA regulations provide flexibility that enables the supply chain to quickly implement the new rule without delay or significant cost.

Modifications necessary for physical security compliance will be a one-time modification primarily to provide for appropriate storage. The DEA understands that handlers of HCPs may also need to make modifications to their current security procedures for compliance. To a lesser extent, there may be necessary modifications to operating procedures, staff training, and amendments to suspicious order monitoring systems. However, due to the high diversion and abuse profile of HCPs, it is reasonably likely that most, if not all, manufacturers and distributors already provide controls and procedures to guard against theft and diversion of HCPs. That is, due to the high diversion potential of HCPs, most, if not all, manufacturers and distributors likely already have operating procedures (e.g., suspicious order monitoring systems, staff training) to guard against theft and diversion of HCPs, thereby necessitating minimal (if any) changes to these non-physical security controls. The DEA

believes that a 45-day period will provide handlers of HCPs a reasonable amount of time to implement any one-time modifications to comply with the DEA regulations. Registrants are familiar with the applicable security regulations, and already have systems in place with respect to other schedule II controlled substances. Accordingly, it is reasonable to revise operating procedures, amend monitoring systems, and train staff with respect to HCPs as schedule II controlled substances within the 45-day compliance timeframe.

The DEA has specifically chosen not to stagger implementation dates of handling requirements for the reasons stated herein. Also, different implementation dates leads to confusion and inconsistent application of the law, particularly with respect to rescheduling a drug from schedule III to schedule II. Schedule II and III substances are subject to different recordkeeping and reporting requirements, for example, and registrants would have difficulty keeping and maintaining records and inventories. Also, if one registrant category were to handle HCPs as schedule III controlled substances while another registrant category were to handle HCPs as schedule II controlled substances, it would be confusing (for the registrants and for enforcement authorities), particularly with respect to the relevant transaction records.

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The DEA strongly advises registrants to work closely with their local DEA office regarding submission of materials, storage containers, all applicable security requirements, and any necessary modifications due to compliance with this rule. **21 CFR 1301.71**(d); see also **21 CFR 1307.03**. After 45 days from the date of publication, HCPs will be subject to schedule II security requirements and must be handled and stored pursuant to **21 U.S.C. 821** and **823** and in accordance with **21 CFR 1301.71-1301.93**.

b. Distribution of C-III Labeled HCPs Post Implementation

The comments of a manufacturer, wholesale distributor, and national trade association comprised of distributors, each discussed their concerns about how commercial containers of HCPs labeled as "C-III" would be handled. The manufacturer requested that the DEA allow at least nine months from the date of issuance of the final rule for distribution of commercial products labeled as "C-III" in order to allow time for the supply chain to be restocked. This same company also requested that the DEA clarify the ability of reverse distributors and other registrants to continue to handle HCPs labeled as "C-III" for at least three months after the expiration date of the substance, in order to account for handling HCPs for purposes of destruction. The wholesale distributor wrote in favor of immediate implementation of the use of DEA Form 222, while allowing HCPs already labeled as C-III to be continuously distributed until depleted.

DEA response: For the reasons discussed in response to the previous comments, as of the effective date of the final rule, pursuant to **21 U.S.C. 821**, **825**, and **958**(e) and in accordance with **21 CFR 1302.03**, manufacturers are required to print upon the labeling of each commercial container of HCPs they distribute the designation of HCPs as "C-II." It shall be unlawful for commercial containers of HCPs to be distributed downstream without bearing the label properly identifying them as schedule II controlled substances in accordance with **21 CFR part 1302**. As clearly stated in **21 CFR 1302.05**, "[a]ll labels on commercial containers of, and all labeling of, a controlled substance which either is transferred to another schedule or is added to any schedule shall comply with the requirements of **Sec. 1302.03**, on or before the effective date established in the final order for the transfer or addition." Accordingly, the DEA is requiring that commercial containers of HCPs distributed on or after 45 days from the date of publication of the final rule be labeled as "C-II" and be packaged in accordance with **21 CFR part 1302**.

A distribution of HCPs on or after the effective date of this final rule, is a distribution of a schedule II controlled substance, and a DEA Form 222 is required to be used to conduct the transfer in accordance with **21 CFR 1305.03**. A registrant may transfer commercial containers of HCPs labeled as "C-III" upstream on or after the effective date of the final rule, with utilization of a DEA Form 222 as required in accordance with 21 CFR 1305.03. Utilization of the DEA Form 222 ensures that schedule I and II controlled substances are accounted for, and allows for the detection and prevention of diversion.

Additionally, as discussed previously in more detail in the Economic Impact Analysis, the DEA believes that any manufacturer or distributor that requires more than 45 days to sell HCP inventory under normal circumstances can make minor modifications to ordering and stocking procedure for a transitional period to meet the established effective date. Distributors also have the option of returning excess stock of HCPs labeled as "C-III" to the manufacturer, or the manufacturer's authorized agent, as authorized by this final rule, or in accordance with 21 CFR 1307.12.

The DEA takes this opportunity to clarify that the regulation pertaining to labeling of commercial containers applies to distributions by manufacturers and distributors. The DEA does not regulate the labeling and packing of commercial containers of controlled substance downstream of distributors.

c. Exemption of Distributors and Manufacturers

A national trade association comprised of distributors and an individual manufacturer of HCPs requested that the DEA provide an exemption from the schedule II controlled substance security requirements for manufacturers and distributors of HCPs. Both commenters based this request on the assertion that manufacturers and distributors are not a documented significant source of diversion.

DEA response: Scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on purported sources of diversion. One of the primary functions of the DEA Diversion Control Program is to ensure that registrants are in compliance with the safeguards inherent in the CSA. This proactive approach is designed to identify and prevent the large scale diversion of controlled substances and listed chemicals into the illicit market. Manufacturers and distributors pose the greatest potential for large- scale diversion. As discussed in the final rule, "Controlled Substances and List I Chemical Registration and Reregistration Fees," there is great risk and grave consequences associated with the quantity and purity of controlled substances and/or chemicals with each manufacturer at this point in the closed system. 77 FR 15234, 15241, March 15, 2012. Accordingly, non-practitioners such as manufacturers and distributors must adhere to very stringent physical security requirements. The DEA has determined that there is a high potential for abuse of HCPs, and this, inter alia, requires that HCPs be controlled in schedule II. The physical security requirements applicable to schedule II controlled substances will provide secure controls to detect and prevent diversion of HCPs. Accordingly, the DEA declines to exempt manufacturers or distributors from the physical security requirements applicable to HCPs upon control in schedule II. However, the DEA encourages manufacturers and distributors to work closely with their local DEA office regarding submission of materials, storage containers, all applicable security requirements, and any necessary modifications due to compliance with this rule. **21 CFR 1301.71**(d); see also **21 CFR 1307.03**.

10. Economic Impact

a. Cost to Ultimate Users

Several commenters stated that the DEA had failed to fully take into account costs and impacts to ultimate users in its economic impact analysis.

DEA response: Scheduling decisions are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on the population it is intended or approved to treat, or potential impacts thereon. However, as

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discussed above, scheduling or rescheduling a drug does not hinder legitimate access to needed medication. For the reasons discussed earlier in this document, the DEA does not believe that there will be significant impacts, if any, on ultimate users associated with this rulemaking.

b. Cost of Physical Security

Several commenters suggested that it would cost millions of dollars for distributors and retail pharmacies to obtain new vaults or increase the size of their vaults to accommodate for the influx of HCPs. Another commenter suggested that only a limited number of firms can build vaults that meet the requirements of the DEA and because of this, constructing a vault would be time consuming and costly.

DEA response: Scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on economic impacts.

Retail pharmacies are not required by the CSA or DEA regulations to place schedule II controlled substances in a vault or safe. In accordance with **21 CFR 1301.75**(b), pharmacies may disperse schedule II controlled substances throughout their stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances.

11. Proposed Alternatives

a. Establishment of a National Prescription Drug Monitoring Program (PDMP)

Several commenters requested the implementation of a national prescription drug monitoring program (PDMP) either as an alternative to rescheduling HCPs, or possibly in addition thereto, as a means of curtailing doctor shopping and preventing abuse. For example, one commenter noted that "Despite broad consensus that prescribers and public health officials need these essential tools modernized to support clinical decision-making and identify state and regional patterns of abuse and diversion, state-based PDMPs continue to have limited financial resources and interoperability * * *." Another commenter stated that PDMPs "can be improved by creating incentives for inter-state connectivity, making data available in a more timely fashion and unifying standard submissions."

DEA response: One of the best ways to combat the rising tide of prescription drug abuse is the implementation and use of PDMPs. PDMPs help prevent and detect diversion and abuse of pharmaceutical controlled substances, particularly at the retail level where no other automated information collection system exists. PDMPs valuable tools for prescribers, pharmacists, and law enforcement agencies to identify, detect, and prevent prescription drug abuse and diversion.

The DEA supports and encourages the development and maintenance of PDMPs at the State level. Currently, 48 States have an operational PDMP (meaning collect data from dispensers and reporting information from the database to authorized users). One State has enacted legislation enabling the program to come online; Missouri has no state PDMP. As of February, 2014, only 16 States mandate usage of PDMP. Of those 16 States, 6 States mandate its usage in designated circumstances and 10 mandate its use in broader circumstances. Currently, 26 States have adopted the Interconnect platform for data sharing.

The DEA agrees with these commenters that the use of PDMPs is challenging across State lines because interconnectivity is limited. Interconnectivity or a nationwide system would help deter and detect drug traffickers and drug seekers, many of whom willingly travel hundreds of miles to gain easy access to unscrupulous pain clinics and physicians.

The Department has supported the development of PDMPs through the Harold Rogers Prescription Drug Monitoring grant program, distributing a total of over $87 million from FY 2002 to FY 2014, including $7 million in FY 2014. The purpose of this program is to enhance the capacity of regulatory and law enforcement agencies to collect and analyze controlled substance prescription data. It focuses on providing help for States that want to establish a PDMP or expand an existing PDMP. In 2012, the Department provided further policy guidance on data sharing efforts among State PDMPs, a critical aspect of the program.

b. Better Utilization of Currently Established State PDMPs Already in Existence

One commenter suggested that State monitoring systems should be used in a way to specifically identify usage of HCPs in the respective State. The commenter stated that this would allow each State to develop its own methods for handling the abuse of HCPs problem rather than making a nationwide rule rescheduling HCPs to schedule II. Another commenter suggested that practitioners should use State prescription monitoring programs more to prevent unnecessary refills and prescriptions, thereby preventing abuse. Another commenter suggested that States should be mandated to implement a PDMP if they don't already have one in existence.

DEA response: As mentioned above, States are free to implement their own PDMP. Moreover, States may customize their PDMP in a way that is most beneficial to that State. The States can do this so long as the laws governing the program do not conflict with the CSA, DEA regulations, or other federal law.

However, the DEA, as required by the CSA, has an obligation to control drugs or other substances that have a potential for abuse. Once the DEA controls a drug or substance, it must apply the provisions of the CSA to that newly controlled drug or substance. As stated, scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b).

c. Establishment of a List of "Vetted Patients"

One commenter suggested "that people who genuinely need the medication * * * be listed in the state monitoring system as patients who have been vetted and should be prescribed the medication without [schedule II] requirements." The commenter proposed that such vetting could be done on a six month renewal basis.

DEA response: The CSA does not prevent the States from enacting laws related to controlled substances or prevent States from creating stricter laws. See **21 U.S.C. 903**. However, States cannot create rules that are more relaxed than the CSA, and its implementing regulations, as this would be a conflict. See Id. Creating a list of vetted patients who do not have to comply with schedule II requirements would be in direct conflict with the CSA and schedule II prescription requirements. An individual practitioner must determine if an individual has a legitimate medical purpose to be issued a prescription for a controlled substance each time a prescription is issued. There is no

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mechanism to "vet" a patient in the CSA.

d. Monitoring and/or Enforcement

One commenter stated that "I believe more effort should go into the monitoring the narcotics registry and targeting [of] patients or doctors that are suspicious for abuse rather than trying to restrict the narcotics given." Another suggested to "vet the patients by 2 different doctor evaluations, vetting to extend for 6 months. Register the vetted patients in the state drug monitoring programs as 'OK' to obtain 90-day supplies. Patients not vetted get a very limited supply."

DEA response: The DEA actively pursues administrative action and civil and criminal prosecution of DEA registrants and individuals who divert controlled substances. One of the primary functions of the DEA Diversion Control Program is to ensure that all DEA registrants are in compliance with the safeguards inherent in the CSA. This proactive approach is designed to identify and prevent diversion of controlled substances and listed chemicals into the illicit market. Insofar as the issuance of and the filling of controlled substance prescriptions is concerned, prescribers and pharmacies, have an obligation to ensure that they do not prescribe or dispense controlled substances to individuals with no legitimate medical purpose for the controlled substance.

e. Change of Prescription Requirements While Retaining Schedule III Status

Several commenters suggested that the DEA change prescription requirements for HCPs while keeping them as schedule III controlled substances instead of transferring them to schedule II of the CSA. For example, some commenters suggested that subcategories be created for specific categories of practitioners, such as oncologists or emergency practitioners. Other commenters suggested that the DEA should limit the quantity of HCPs prescribed or number of refills authorized instead of rescheduling HCPs. As an example, one commenter suggested that any HCP prescriptions of 30 tablets and under should remain as a schedule III controlled substance and prescriptions for over 30 tablets of HCPs should be a schedule II controlled substance.

DEA response: The DEA cannot retain schedule III status for HCPs, as the DEA has determined that HCPs satisfy the criteria for control in schedule II of the CSA. **21 U.S.C. 812**(b).

The Assistant Secretary of the HHS provided a scientific and medical evaluation and a scheduling recommendation to control HCPs as a schedule II controlled substance. In accordance with **21 U.S.C. 811**(c), the DEA conducted its own analysis of the eight factors determinative of control. Besides published literature, various other data as detailed in the supporting documents were considered in making the scheduling determination for HCPs. Thus, the scheduling determination is based on a comprehensive evaluation of all available data as related to the required eight factors. The summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at http://www.regulations.gov under Docket No. DEA-389. Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that HCPs have an abuse potential and meets the requirements for schedule II controls under the CSA.

f. Education of Prescribing Practitioners

Several commenters suggested that prescribing practitioners should receive education about the problems of HCP abuse, addiction, and prevention of diversion rather than rescheduling HCPs.

DEA response: The DEA fully supports efforts by medical professionals, acting alone and as part of professional organizations, as well as industry associations, to educate members of their profession/industry on the risks associated with prescription opioid use and on ways to prevent misuse, abuse, and diversion of prescription opioid products. These efforts are an important and integral part of tackling the problem of prescription opioid abuse.

However, as recognized by the CDC, the United States is in the midst of a public health crisis regarding prescription painkiller overdose. Individuals, families, and society are suffering the effects of abuse and addiction. People are dying. In their 2011 report, the CDC estimated that 75 opioid-related deaths occur each day. This equates to over 27,000 people each year. As a society, America simply cannot afford to wait for self-initiated educational programs and measures by medical professionals and industry to solve the problem on their own. As acknowledged by commenters advocating solely for an educational approach, opioid consumption in the United States continues to increase despite self-initiated professional educational endeavors such as symposia and scientific articles.

One physician who wrote in support of rescheduling asserted that only a limited number of practitioners have paid attention to the warnings issued regarding the risk of addiction, overdose, and death associated with use of HCPs. It was this physician's belief that: "The opioid epidemic has mainly resulted from a large volume of

misinformed doctors failing to understand the risks and limited benefits of these drugs, especially for chronic noncancer pain, one of the most common reasons why patients seek medical care." This concern has been echoed by the HHS. The HHS has noted "Multiple studies have shown that a small percentage of prescribers are responsible for prescribing the majority of opioids." Behavioral Health Coordinating Committee, Prescription Drug Abuse Subcommittee, HHS. Addressing Prescription Drug Abuse in the United States: Current Activities and Future Opportunities. 2013. (internal citations omitted). The HHS points out, however, that "Providers who are not high-volume prescribers may also contribute to opioid abuse and overdose because of a lack of education and awareness about appropriate opioid prescribing * * *." The HHS additionally stated, "Even when sufficient information exists, studies show that some providers do not follow risk mitigation strategies even for patients known to be at high risk for abuse." Id. The physician- commenter asserted that "Upscheduling hydrocodone combination products will, at the very least, send a clear message to these providers that hydrocodone is a narcotic in the same class as oxycodone, morphine and heroin, which should be prescribed and refilled with the utmost of selectivity, caution and close patient follow-up."

The problem must be addressed both nationally and locally by using all available legal and social measures at hand. At the Federal level, this includes following the legal path directed by Congress to address issues of substance abuse and trafficking. As part of a comprehensive approach involving multiple Federal and State actors to address these concerns, Congress has charged the DEA with the responsibility to implement and enforce, to the fullest extent of the law, the requirements of the CSA. This includes ensuring that drugs and other substances are appropriately scheduled concordant with the factors for each schedule under **21 U.S.C. 812**(b).

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g. Education and Rehabilitation of Ultimate Users

Several commenters suggested that patient education and/or rehabilitation was the proper route to address abuse of HCPs rather than rescheduling.

DEA response: A multi-pronged approach, one that includes education, treatment, monitoring, and law enforcement is needed to combat this epidemic. The DEA supports all efforts to educate patients about the risks associated with use of substances with abuse potential. As discussed above, an analysis of the eight factors determinative of control demonstrates that HCPs warrant control II of the CSA. **21 U.S.C. 812**(b).

h. Strict Enforcement/Sanctions

Several commenters voiced an opinion that there should be strict enforcement against those that have diverted and illegally sold prescription HCPs. These commenters stated it would be a good idea to ban these offenders from receiving HCPs or reduce limits on how much HCPs an offender can receive. In addition, several commenters suggested tougher sanctions and enforcement should be applied to providers who are not lawfully practicing their trade rather than punishing those who are obeying the laws.

DEA response: The DEA mission is to implement and enforce the CSA and corresponding regulations to the fullest extent of the law. The DEA actively pursues administrative action and civil and criminal prosecution of DEA registrants and other individuals who divert controlled substances. One of the primary functions of the DEA Diversion Control Program is to ensure that registrants are in compliance with the safeguards inherent in the CSA. The DEA supports State and local law enforcement, and State professional and regulatory boards in their efforts to prevent diversion and enforce the controlled substances laws.

V. Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of HCPs. As such, the DEA is rescheduling HCPs as a schedule II controlled substance under the CSA.

VI. Determination of Appropriate Schedule

The CSA outlines the findings required to transfer a drug or other substance between schedules (I, II, III, IV, or V) of the CSA. **21 U.S.C. 811**(a); **21 U.S.C. 812**(b). After consideration of the analysis and rescheduling recommendation of the Assistant Secretary for Health of the HHS and review of available data, the Administrator of the DEA, pursuant to **21 U.S.C. 811**(a) and **21 U.S.C. 812**(b)(2), finds that:

1. HCPs have a high potential for abuse. The abuse potential of HCPs is comparable to the schedule II controlled substance oxycodone;

2. HCPs have a currently accepted medical use in treatment in the United States. Several pharmaceutical products containing hydrocodone in combination with acetaminophen, aspirin, other NSAIDs, and homatropine are approved by the FDA for use as analgesics for pain relief and for the symptomatic relief of cough and upper respiratory symptoms associated with allergies and colds; and

3. Abuse of HCPs may lead to severe psychological or physical dependence.

Based on these findings, the Administrator of the DEA concludes that HCPs warrant control in schedule II of the CSA. **21 U.S.C. 812**(b)(2).

VII. Requirements for Handling HCPs

Upon the effective date of this final rule, any person who handles HCPs will be subject to the CSA's schedule II regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engaging in research, conducting instructional activities, and conducting chemical analysis, of schedule II controlled substances, including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, conducts instructional activities with, or conducts chemical analysis with) HCPs, or who desires to handle HCPs, must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of October 6, 2014.

Security. HCPs are subject to schedule II security requirements and must be handled and stored pursuant to **21 U.S.C. 821** and **823**, and in accordance with **21 CFR 1301.71-1301.93** as of October 6, 2014.

Labeling and Packaging. All labels, labeling, and packaging for commercial containers of HCPs must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302** as of October 6, 2014, except with respect to exchanges for purposes of relabeling/ repackaging as provided below under "Quotas."

Quotas. A quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** is required in order to manufacture HCPs as of October 6, 2014. Registrants required to obtain an individual manufacturing quota shall not manufacture HCPs on or after October 6, 2014, unless an individual manufacturing quota is granted for such quantities of HCP to be manufactured. Registrants required to obtain a procurement quota shall not procure HCPs on or after October 6, 2014, unless a procurement quota is granted for such quantities of HCP to be procured.

Except, registrants authorized to manufacture schedule II and III controlled substances may relabel/repackage HCPs labeled as "CIII" or "C-III" without obtaining procurement quota for such activity, under the following conditions:

(1) The manufacturing activity occurs before December 8, 2014;

(2) if the manufacturer is relabeling/repackaging HCPs that were returned to the manufacturer, the manufacturer returns the same quantity and strength of HCPs labeled as "CII" or "C-II" back to the registrant that returned HCPs labeled as "CIII" or "C-III" to the manufacturer; and

(3) an invoice or the DEA Form 222 (whichever is applicable) records the transfer and reflects that the transfer occurred pursuant to the authority contained in this final rule.

For example, if before October 6, 2014, distributor A transfers 5 packages of 100-bottle 5/325 HCPs labeled as CIII/C-III to manufacturer B, solely for the purpose of relabeling, the invoice would reflect that the transfer occurred pursuant to the authority in this final rule. If the return occurs after October 6, 2014, the DEA Form 222 would reflect that the transfer occurred pursuant to the authority contained in this final rule. When the manufacturer distributes HCPs labeled as "CII" or C-II" back to the registrant that returned the HCPs labeled as "CIII" or "C-III," the manufacturer must return the same quantity and strength that was originally received for relabeling/repackaging. The DEA Form 222 will, again, reflect that the transfer occurred pursuant to the authority contained in this final rule.

In the above example, the manufacturer would not be required to obtain a procurement quota in order to relabel/repackage 5 packages of 100-bottle 5/325 HCPs, so long as

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manufacturer B subsequently transfers to distributor A 5 packages of 100-bottle 5/325 HCPs labeled as CII/C-II, unless the relabel/repackage activity occurs after December 8, 2014.

Registrants may continue to return HCPs pursuant to 21 CFR 1307.12.

Inventory. Any person who becomes registered with the DEA on or after the effective date of the final rule must take an initial inventory of all stocks of controlled substances (including HCPs) on hand on the date the registrant first engages in the handling of controlled substances pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b) as of October 6, 2014.

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including HCPs) on hand every two years pursua **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records and Reports. Every DEA registrant must maintain records and submit reports with respect to HCPs pursuant to **21 U.S.C. 827** and **958**, and in accordan with **21 CFR parts 1304** and **1312** as of October 6, 2014. Each pharmacy with a modified registration under **21 U.S.C. 823**(f) that authorizes the dispensing of controlled substances by means of the Internet must submit reports to the DEA regarding HCPs pursuant to **21 U.S.C. 827** and in accordance with **21 CFR 1304.55** as of October 6, 2014.

Orders for HCPs. Every DEA registrant who distributes HCPs must comply with order form requirements, pursuant to **21 U.S.C. 821**, **828**, **871** and in accordance with **21 CFR parts 1305** and **1307** as of October 6, 2014.

Prescriptions. All prescriptions for HCPs must comply with **21 U.S.C. 829**(a) and must be issued in accordance with **21 CFR part 1306** and subpart C of **21 CFR part 1311** as of October 6, 2014. No prescription for HCPs issued on or after October 6, 2014 shall authorize any refills. Any prescriptions for HCPs that are issued before October 6, 2014, and authorized for refilling, may be dispensed in accordance with **21 CFR 1306.22-1306.23**, **1306.25**, and **1306.27**, if such dispensing occurs before April 8, 2015.

Importation and Exportation. All importation and exportation of HCPs must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and in accordance with **21 CFR part 1312** as of October 6, 2014.

Liability. Any activity involving HCPs not authorized by, or in violation of, the CSA or its implementing regulations, occurring as of October 6, 2014, is unlawful, and may subject the person to administrative, civil, and/or criminal action.

VIII. 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 performed "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 procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) 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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612) (RFA), has reviewed this rule, and by approving it, certifies that it will not a significant economic impact on a substantial number of small entities. The purpose of this rule is to place HCPs into schedule II of the CSA. No less restrictive measures (i.e., non-control or control in a lower schedule) would enable the DEA to meet its statutory obligation under the CSA.

HCPs are widely prescribed drugs for the treatment of pain and cough suppression. Handlers of HCPs primarily include manufacturers, distributors, exporters, pharmacies, practitioners, mid-level practitioners, and hospitals/clinics.\30\ It is possible that other registrants, such as importers, researchers, analytical labs, teaching institutions, etc., also handle HCPs. However, based on its understanding of its registrant population, the DEA assumes for purposes of this analysis that for all business activities other than manufacturers, distributors, exporters, pharmacies, practitioners, mid- level practitioners, and hospitals/clinics, that the volume of HCPs handled is nominal, and therefore de minimis to the economic impact determination of this rescheduling action.

\30\ For purposes of performing regulatory analysis, the DEA uses the definition of a "practitioner" as a physician, veterinarian, or other individual licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he/she practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, pharmacy, or hospital (or other person other than an individual). For the purposes of performing regulatory analysis, "mid-level practitioner" means an individual registered with the DEA as a "mid-level practitioner" but does not include practitioners as defined above. Examples of mid-level practitioners include, but are not limited to, health care providers such as nurse practitioners, nurse midwives, nurse anesthetists, clinical nurse specialists and physician assistants.

Because HCPs are so widely prescribed, for the purposes of this analysis, the DEA conservatively assumes all distributors, exporters, pharmacies, practitioners, mid-level practitioners, and hospitals/ clinics currently registered with the DEA to handle schedule III controlled substances are also handlers of HCPs. The DEA estimated the number of manufacturers and exporters handling HCPs directly from DEA records. In total, the DEA estimates that nearly 1.5 million controlled substance registrations, representing approximately 376,189 entities, would be affected by this rule.

The DEA does not collect data on company size of its registrants. The DEA used DEA records and multiple subscription-based and public data sources to relate the number of registrations to the number of entities and the number of entities that are small entities. The DEA estimates that of the 376,189 entities that would be affected by this rule, 366,351 \31\ are "small entities" in accordance with the RFA and Small Business Administration size

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standards. 5 U.S.C. 601(6); 15 U.S.C. 632.

\31\ The estimated break-down is as follows: 50 manufacturers; 4 exporters; 683 distributors; 50,774 pharmacies; and 314,840 persons registered as or employing practitioners/mid-level practitioners/ hospitals/clinics.

The DEA examined the registration, security (including storage), labeling and packaging, quota, inventory, recordkeeping and reporting, ordering, prescribing, importing, exporting, and disposal requirements for the 366,351 small entities estimated to be affected by the rule. The DEA estimates that only the physical se requirements will have material economic impact and such impacts will be limited to manufacturers, exporters, and distributors. Many manufacturers and export are likely to have sufficient space in their existing vaults to accommodate HCPs. However, the DEA understands that some manufacturers, exporters, and distribu will need to build new vaults or expand existing vaults to store HCPs in compliance with schedule II controlled substance physical security requirements. Due to the uniqueness of each business, the DEA made assumptions based on research and institutional knowledge of its registrant community to quantify the costs associated with physical security requirements for manufacturers, exporters and distributors.

The DEA estimates there will be significant economic impact on 1 (2.0%) of the affected 50 small business manufacturers, and 54 (7.9%) of the affected 683 small business distributors. The DEA estimates no significant impact on the remaining affected 4 small business exporters, 50,774 small business pharmacies, or 314,840 small business practitioners/mid-level practitioners/hospitals/clinics.

In summary, 55 of the 366,351 (0.015%) affected small entities are estimated to experience significant impact, (i.e., incur costs greater than 1% of annual revenue) as a result of this rule being finalized. The percentage of small entities with significant economic impact is below the 30% threshold for all registrant business activities. The DEA's assessment of economic impact by size category indicates that the rule to reschedule HCPs as schedule II controlled substances will not have a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, the DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year * * *." Therefore, neither a Small Government agency Plan nor any other action is required under provisions of the UMRA 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). This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 amended as follows:

PART 1308--SCHEDULES 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.

Sec. 1308.13 [Amended]

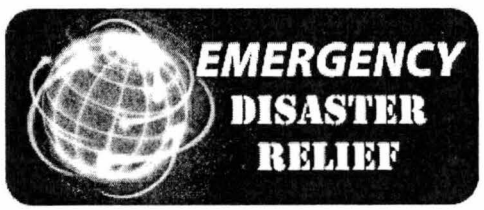
- 2. Amend **Sec. 1308.13** by removing paragraphs (e)(1)(iii) and (iv) and redesignating paragraphs (e)(1)(v) through (viii) as (e)(1)(iii) through (vi), respectively.

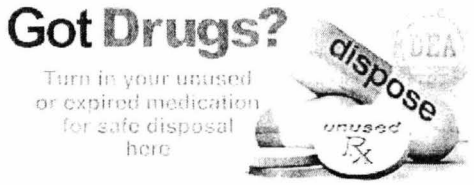
Dated: August 15, 2014.

Michele M. Leonhart,
Administrator.

[FR Doc. 2014-19922 Filed 8-21-14; 8:45 am]

BILLING CODE 4410-09-P





Rules - 2014

[Federal Register Volume 79, Number 39 (Thursday, February 27, 2014)]
[Rules and Regulations]
[Pages 10985-10989]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014-04332]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-370]

Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV

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 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, or possess) or propose to handle alfaxalone and substances containing alfaxalone.

DATES: Effective Date: March 31, 2014.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, controlled substances are classified into 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 established by Congress are found at 21 U.S.C. 812(c), and the current list of all 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 [**21 U.S.C. 812**(b)] 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 the DEA. 28 CFR 0.104.

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 the Department of Health and Human Services (HHS),\1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action is based on a recommendation from the Assistant Secretary of the HHS and on an evaluation of all other relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle or propose to handle alfaxalone.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1995. In addition, because the Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations, for purposes of this document, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

Background

Alfaxalone (5[alpha]-pregnan-3[alpha]-ol-11,20-dione, previously spelled "alphaxalone"), a substance with central nervous system (CNS) depressant properties, is a neurosteroid that is a derivative of 11-alpha-hydroxy-progesterone. On October 23, 2012, the Food and Drug Administration (FDA) published a final rule to approve a New Animal Drug Application (NADA, 141-342) for alfaxalone (Alfaxan[supreg]), as an intravenous injectable anesthetic, for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance of anesthesia with an inhalant anesthetic, in cats and dogs (77 FR 64715). Alfaxalone primarily

acts as an agonist at the gamma-aminobutyric acid (GABA) receptor-channel complex, with a mechanism of action at this site similar to that of barbiturates like phenobarbital (schedule IV) and methohexital (schedule IV), benzodiazepines such as diazepam (schedule IV) and midazolam (schedule IV), as well as the anesthetic agents

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propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol (schedule IV).

HHS and DEA Eight-Factor Analyses

On July 17, 2012, the Assistant Secretary of the HHS provided to the DEA a scientific and medical evaluation and scheduling recommendation entitled "Basis for the Recommendation to Control Alfaxalone in Schedule IV of the Controlled Substances Act." After considering the eight factors in **21 U.S.C. 811**(c), including consideration of the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that alfaxalone be controlled in schedule IV of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eight-factor analysis of alfaxalone pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket Number DEA-370) at www.regulations.gov under "Supporting and Related Material."

Determination to Schedule Alfaxalone

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV" which proposed placement of alfaxalone in schedule IV of the CSA. 78 FR 17895, March 25, 2013. The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by April 24, 2013. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before April 24, 2013.

Comments Received

The DEA received four comments on the proposed rule to schedule alfaxalone. Two commenters were in favor of controlling alfaxalone as a schedule IV controlled substance. One commenter was in favor of controlling alfaxalone as a schedule V controlled substance rather than a schedule IV controlled substance, and one commenter opposed the control of alfaxalone.

Support of the Proposed Rule:

Two commenters supported controlling alfaxalone as a schedule IV controlled substance. These commenters indicated support for controlling alfaxalone under the CSA based on the abuse potential of the substance. Because alfaxalone is indicated for use as a pre-anesthetic and anesthetic in cats and dogs, these commenters felt that the abuse potential was particularly high for persons with access to the substance in the medical field. One commenter noted that controlling alfaxalone as a schedule IV controlled substance is appropriate because it could be abused in a manner similar to other schedule IV CNS depressants. The commenters believe that controlling alfaxalone as a schedule IV controlled substance will provide the necessary controls to prevent its diversion.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

Opposition to the Proposed Rule:

Two commenters opposed the proposal to control alfaxalone as a schedule IV controlled substance.

Request Not to Control Alfaxalone:

One commenter opposed controlling alfaxalone at all and stated that alfaxalone does not have the same abuse potential as Xanax[supreg] (alprazolam) (schedule IV), Valium[supreg] (diazepam) (schedule IV), and other benzodiazepines. The commenter also stated that controlling alfaxalone under the CSA would make it difficult for veterinarians and animal surgeons to acquire the drug. Lastly, this commenter stated that alfaxalone is "unheard of outside of the veterinary community and does not have a 'black market' as do the other schedule IV drugs."

DEA Response: The DEA does not agree. 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." This scheduling action was initiated when the DEA received a scientific and medical evaluation and a scheduling recommendation to control alfaxalone as a schedule IV controlled substance from the Assistant Secretary of the HHS. In accordance with 21 U.S.C. 811(c), the DEA conducted its own analysis of the eight factors determinative of control or removal: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. The summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at www.regulations.gov under Docket Number DEA-370.

Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that alfaxalone has an abuse potential similar to other schedule IV drugs, including the benzodiazepines diazepam and midazolam, the barbiturates phenobarbital and methohexital, and also the anesthetic agents propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol. Alfaxalone also acts as an agonist at the gamma-aminobutyric acid (GABA) receptor-channel complex, with a mechanism of action at the site similar to that of benzodiazepines like diazepam(schedule IV) and midazolam (schedule IV). This mechanism of action is also similar to that of other schedule IV controlled substances, including barbiturates like phenobarbital and methohexital, and also anesthetic agents like propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol. It should be noted that alfaxalone's current exclusive use as a veterinary anesthetic drug and the asserted conclusion that there is no "black market" for the substance, do not negate its abuse potential and associated risk of diversion. The DEA and HHS analyses demonstrate that alfaxalone does have the potential for abuse and meets the necessary findings on potential for abuse, currently accepted medical use, and physical or psychological dependence for placement in schedule IV. Burdens associated with acquiring a substance as a result of control under the CSA are not relevant factors to the determination whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, the DEA disagrees with the unsupported statement that making alfaxalone a controlled substance would make it difficult for veterinarians and animal surgeons to

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acquire the drug. Several other anesthetic substances used by veterinarians and other practitioners are controlled under the CSA. All veterinarians and animal surgeons who are authorized by the State in which they practice to handle alfaxalone and who are registered with the DEA to dispense controlled substances may acquire alfaxalone once it is controlled. As discussed in the Regulatory Flexibility Analysis section of this document, currently 98% of DEA registrants (most of which are small businesses) are already authorized to handle schedule IV controlled substances.

Request to Control Alfaxalone as a Schedule V Substance:

One commenter stated that alfaxalone should be controlled as a schedule V controlled substance. This commenter stated that there was limited information available regarding alfaxalone's abuse. The commenter also stated that alfaxalone is a new introduction to the United States veterinary market, and controlling it in the least stringent schedule, schedule V, would minimize burdens on practitioners using it for legitimate purposes, while also imposing controls to account for its abuse potential.

DEA Response: The DEA does not agree. The DEA thoroughly reviewed the scientific and medical evaluation and the scheduling recommendation to control alfaxalone as a schedule IV controlled substance from the HHS.

Additionally, the DEA conducted its own analysis of the eight factors in accordance with **21 U.S.C. 811**(b) and made the findings required under **21 U.S.C. 812**(b) for the placement of alfaxalone in schedule IV. Based on the review of the HHS's evaluation and scheduling recommendation and all other relevant and available data, the DEA found that alfaxalone has an abuse potential similar to other schedule IV controlled substances, including the benzodiazepines diazepam and midazolam,

barbiturates phenobarbital and methohexital, and also the anesthetic agents propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol.

While not relevant to the substance's schedule placement, the DEA does not agree with this commenter's concern that the requirements applicable to schedule IV controlled substances are more burdensome than the requirements applicable to schedule V controlled substances. There are only very minimal differences in handling requirements between schedule IV and schedule V controlled substances. Most importantly for purposes of responding to this comment, the physical security requirements for schedule IV and V controlled substances are the same. Also, under the CSA, schedule V controlled substances may be dispensed without a prescription, while schedule IV controlled substances may only be dispensed pursuant to a prescription. However, this distinction is of no consequence with regard to alfaxalone because alfaxalone cannot be prescribed by a veterinarian, nor may alfaxalone be dispensed by a pharmacist pursuant to a prescription. Federal law restricts this drug to use by or on the order of a licensed veterinarian (i.e., it may only be administered). 21 CFR 522.52; see also 21 CFR 514.8.

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of alfaxalone. As such, the DEA is scheduling alfaxalone 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 CSA outlines the findings required for placing 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 the HHS and review of all available data, the Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

> (1) 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) has a low potential for abuse relative to the drugs or other substances in schedule III; the overall abuse potential of alfaxalone is comparable to the schedule IV controlled substances diazepam, midazolam, phenobarbital, methohexital, propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010), and fospropofol;
>
> (2) 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) has a currently accepted medical use in treatment in the United States; alfaxalone was approved for marketing by the FDA as a veterinary anesthetic product for the induction and maintenance of anesthesia in cats and in dogs; and
>
> (3) Abuse of 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

Based on these findings, the Administrator of the DEA concludes that alfaxalone, including its salts, isomers, and salts of isomers, warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Alfaxalone

Upon the effective date of this final rule, any person who handles alfaxalone is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement in research, and conduct of instructional activities, of schedule IV controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) alfaxalone, or who desires to handle alfaxalone, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957** and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of March 31, 2014. Any person who currently handles alfaxalone and is not registered with the DEA must submit an application for registration and may not continue to handle alfaxalone as of March 31, 2014 unless the DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Security. Alfaxalone is subject to schedule III-V security requirements and must be handled and stored pursuant to **21 U.S.C. 821**, **823**, and **871**(b) and in accordance with **21 CFR 1301.71-1301.93**, as of March 31, 2014.

Labeling and Packaging. All labels and labeling for commercial containers of alfaxalone must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302**, as of March 31, 2014.

Inventory. Every DEA registrant who possesses any quantity of alfaxalone on the effective date of this final rule must to take an inventory of all stocks of alfaxalone on hand as of March 31, 2014, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d).

Any person who becomes registered with the DEA after March 31, 2014 must take an initial inventory of all stocks of controlled substances (including alfaxalone) on hand on the date the registrant first engages in the handling

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of controlled substances, pursuant to **21 U.S.C. 827** and **958** and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b).

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including alfaxalone) on hand every two years, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records. All DEA registrants must maintain records with respect to alfaxalone pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304**, **1307**, and **1312**, as of March 31, 2014.

Prescriptions. The DEA recognizes that alfaxalone is currently only approved as an injectable anesthetic that is administered to patients. The DEA also acknowledges that Federal law currently restricts alfaxalone to use by or on the order of a licensed veterinarian, and it may not be dispensed pursuant to a prescription. 21 CFR 522.52; see also 21 CFR 514.8. A "prescription" is defined as an order for medication which is dispensed to or for an ultimate user but does not include an order for medication which is dispensed for immediate administration to the ultimate user (e.g., an order to dispense a drug to a bed patient for immediate administration in a hospital is not a prescription). **21 CFR 1300.01**(b). However, any lawful prescriptions for alfaxalone or prescriptions for products containing alfaxalone must comply with **21 U.S.C. 829** and must be issued in accordance with **21 CFR parts 1306** and **1311 subpart C** as of March 31, 2014.

Importation and Exportation. All importation and exportation of alfaxalone must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and be in accordance with **21 CFR part 1312** as of March 31, 2014.

Criminal Liability. Any activity involving alfaxalone not authorized by, or in violation of, the CSA, occurring as of March 31, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612), has reviewed this final rule and by approving it certifies that it will have a significant economic impact on a substantial number of small entities. The purpose of this final rule is to place alfaxalone, including its salts, isomers, and salts of isomers, into schedule IV of the CSA. By this final rule, alfaxalone will remain in schedule IV unless and until additional scheduling action is taken to either transfer it between the schedules or to remove it from the list of schedules. See **21 U.S.C. 811** and **812**. No less restrictive measures (i.e., no control or control in schedule V) will enable the DEA to meet its statutory obligations under the CSA.

On September 6, 2012, the FDA approved for use in the United States one product containing alfaxalone, which will have FDA marketing exclusivity and patent protection for several years. Accordingly, the number of currently identifiable manufacturers, distributors, importers, and exporters for alfaxalone is extremely small. The manufacturer who obtained FDA approval for the sale of alfaxalone product in the United States is not considered a "small entity" in accordance with the RFA and Small Business Administration (SBA) size standards. Upon expiration of the exclusivity period, and more likely, the related patent, additional products containing alfaxalone may receive approvals from the FDA, and thus additional manufacturers, distributors, importers, and exporters will handle alfaxalone. Whether such manufacturers, distributors, importers, or exporters may qualify as small entities cannot be determined at this time.

There are currently approximately 1.5 million controlled substance registrations, representing approximately 381,000 entities. The DEA estimates that 371,000 (97%) of these entities are considered "small entities" in accordance with the RFA and SBA size standards. 5 U.S.C. 601(6) and 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the dispensing rates of new chemical entities, the DEA is unable to determine the number of small entities which might handle alfaxalone. However, because alfaxalone is a new chemical entity that is a veterinary anesthetic administered in veterinary settings and is not prescribed to ultimate users, the number of entities affected by the rule would be far fewer than the 381,000 entities represented by all DEA registrants. There are approximately 66,361 veterinarian practitioners and 23 veterinarian distributors (schedules III-V) registered with the DEA.

Despite the fact that the number of small entities possibly impacted by this rule could not be determined, the DEA concludes that they would not experience a significant economic impact as a result of this rule. The DEA estimates all anticipated alfaxalone handlers to be DEA registrants, and currently 98% of DEA registrants (most of which are small entities) are authorized to handle schedule IV controlled substances. Even assuming that all of these registrants were to handle alfaxalone (e.g., practitioners administer the substance), the costs that they would incur as a result of alfaxalone's scheduling would be nominal.

Registrants that dispense (e.g., administer) alfaxalone are expected to incur nominal additional security, inventory, and recordkeeping costs. These registered entities have already established and implemented the systems and processes required to handle schedule IV controlled

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substances and can easily absorb the costs of administering alfaxalone with nominal to no additional economic burden. For example, because DEA-veterinary practitioners are likely to already be schedule IV handlers, they already secure schedule II-V controlled substances in a securely locked, substantially constructed cabinet. See **21 CFR 1301.75**(b). Accordingly, the requirement to secure all controlled substances containing alfaxalone would not impose a significant economic burden upon DEA-registered practitioners as the infrastructure and materials for doing so are already in place. Labeling their products is routine and in the normal course of business of manufacturers. The DEA therefore assumes that the cost of compliance with **21 CFR part 1302** as a result of this final rule is nominal. Correspondingly, the DEA estimates that the cost of the labeling and packaging requirements of this final rule is nominal for the authorized manufacturer. Accordingly, compliance would not require significant additional manpower, capital investment, or recordkeeping burdens.

Because of these facts, this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100,000,000 or more (adjusted for inflation) in any one year * * * ." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA 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. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 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. Amend **Sec. 1308.14** by redesignating paragraphs (c)(1) through (c)(53) as paragraphs (c)(2) through (c)(54) and adding new paragraph (c)(1) to read as follows:

Sec. 1308.14 Schedule IV.

* * * * *

(c) * * *

(1) Alfaxalone—(2731)

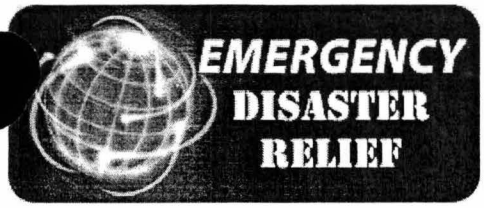
* * * * *

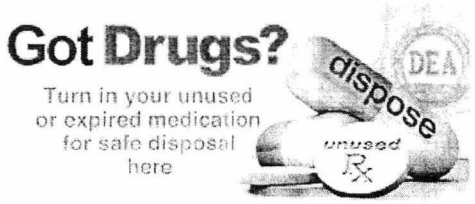
Dated: February 21, 2014.

Michele M. Leonhart,
Administrator.

[FR Doc. 2014-04332 Filed 2-26-14; 8:45 am]

BILLING CODE 4410-09-P





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[Federal Register Volume 79, Number 167 (Thursday, August 28, 2014)]
[Rules and Regulations]
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[FR Doc No: 2014-20515]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-381]

Schedules of Controlled Substances: Placement of Suvorexant into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Deputy Administrator of the Drug Enforcement Administration (DEA) places the substance [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess), or propose to handle suvorexant.

DATES: Effective Date: September 29, 2014.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the substance may cause. **21 U.S.C. 812**. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." The Attorney General has delegated this authority to the Administrator of the DEA, 28 CFR 0.100, who in turn has redelegated that authority to the Deputy Administrator of the DEA. 28 CFR part 0, appendix to subpart R.

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 Health and Human Services (HHS); \1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action imposes the regulatory controls and administrative, civil, and criminal sanctions of schedule IV controlled substances on persons who handle or propose to handle suvorexant.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations.

Background

Suvorexant ([(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone), also known as MK-4305, is a new chemical entity developed for the treatment of insomnia. Suvorexant is a novel, first in class, orexin receptor antagonist with a

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mechanism of action distinct from any marketed drug. It acts via inhibition of the orexin 1 (OX1) and orexin 2 (OX2) receptors. In pharmacological activity studies, suvorexant functioned as an antagonist as demonstrated by its ability to block agonist-induced calcium (Ca\2+\) release. The U.S. Food and Drug Administration (FDA) approved the new drug application for suvorexant on August 13, 2014.

DEA and HHS Eight Factor Analyses

On June 27, 2013, the HHS provided the DEA with a scientific and medical evaluation document prepared by the FDA entitled "Basis for the Recommendation to Place Suvorexant in Schedule IV of the Controlled Substances Act." After considering the eight factors in **21 U.S.C. 811**(c), including consideration of the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that suvorexant be controlled in schedule IV of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eightfactor analysis of suvorexant pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket Number DEA-381) at http://www.regulations.gov under "Supporting and Related Material."

Determination to Schedule Suvorexant

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Deputy Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Suvorexant into Schedule IV" which proposed placement of suvorexant in schedule IV of the CSA. 79 FR 8639, Feb. 13, 2014. The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by March 17, 2014. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before March 17, 2014.

Comments Received

The DEA received five comments on the proposed rule to schedule suvorexant. Two commenters supported controlling suvorexant as a schedule IV controlled substance. One commenter opposed the control of suvorexant, one commenter did not articulate an official position, and one commenter was in favor of controlling suvorexant as a schedule III controlled substance, rather than a schedule IV controlled substance.

Support for the Proposed Rule

Two commenters supported controlling suvorexant as a schedule IV controlled substance. These commenters indicated support for controlling suvorexant under the CSA based on the abuse potential of the substance. The commenters noted that controlling suvorexant as a schedule IV controlled substance is appropriate because it is similar to zolpidem (schedule IV), while one commenter stated that suvorexant produces fewer adverse effects than zolpidem. The commenters believe that controlling suvorexant as a schedule IV controlled substance will provide the necessary controls to prevent its diversion.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

Opposition to the Proposed Rule

Two commenters opposed the proposal to control suvorexant as a schedule IV controlled substance, and one commenter did not articulate an official position but expressed concern about the side effects of suvorexant.

Request Not To Control Suvorexant

One commenter opposed controlling suvorexant because they believed that there was a lack of strong scientific evidence that suvorexant has been abused, and the comparison of suvorexant with zolpidem (schedule IV) is incorrect due to each compound eliciting its effects via different mechanisms of action. The commenter was also concerned that controlling suvorexant will make it more difficult for patients to obtain the substance once it is approved by the FDA.

DEA Response: The DEA does not agree. Suvorexant is a novel, first in class, new chemical substance and information on actual abuse data is not currently available. The legislative history of the CSA addresses the assessment of a new drug's potential for abuse,\2\ and data from clinical studies investigating the abuse potential for suvorexant suggests that its effect is similar to zolpidem (schedule IV). Similarly, while the mechanism of action for suvorexant is distinct from any currently marketed drug for insomnia, human abuse potential studies demonstrated that suvorexant produced effects that were indistinguishable from zolpidem (schedule IV).

\2\ The legislative history of the CSA provides that a substance may have a potential for abuse if: "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." Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444 (1970); as reprinted in 1970 U.S.C.C.A.N. 4566, 4601.

Burdens associated with acquiring a substance as a result of control under the CSA are not relevant factors to the determination whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, the DEA disagrees with the unsupported statement that making suvorexant a controlled substance will make it difficult for ultimate users to legally acquire the substance once it is approved by the FDA. If a DEA-registered practitioner lawfully prescribes suvorexant to treat a medical condition, it may be dispensed on the basis of an oral or written prescription. **21 CFR 1306.04**(a), **1306.21**.

Request To Control Suvorexant as a Schedule III Substance

One commenter had multiple concerns regarding the placement of suvorexant in schedule IV. The commenter believed that further studies on minimal levels of effective suvorexant doses should be conducted to reduce the risks of driving accidents. The commenter also expressed concern about the FDA's statement that while effective, suvorexant is unsafe at various doses. This commenter believed that due to lack of conclusive findings, suvorexant should be categorized as a schedule III controlled substance for "safety and precautionary purposes" since it is a novel, first in class, new substance.

Another commenter, who did not articulate a specific position, expressed concern that the side effects produced by suvorexant were similar to the effects of sleep deprivation, including cognitive and psychomotor impairment.

DEA Response: The concerns about the limited research on minimal levels of effective suvorexant doses and the side effects of suvorexant and sleep deprivation, along with the statement that suvorexant is unsafe at various doses, are outside the scope of the DEA's scheduling authority. As part of the new drug approval process, the HHS

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provides scientific and medical evaluations of a drug or other substance to ensure that it is safe and effective for its intended use. This process is completely separate from the DEA's proceedings to control such drug or other substance. **21 U.S.C. 811**.

The DEA does not agree that suvorexant should be controlled as a schedule III controlled substance. 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." This scheduling action was initiated when the DEA received a scientific and medical evaluation and a scheduling recommendation to control suvorexant as a schedule IV controlled substance from the Assistant Secretary of the HHS. In accordance with 21 U.S.C. 811(c), the DEA conducted its own analysis of the eight factors determinative of control or removal: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. The summary of each factor as analyzed by the DEA and the HHS, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at http://www.regulations.gov under Docket Number DEA-381.

There is evidence that suvorexant has a potential for abuse comparable to zolpidem (schedule IV), and like zolpidem, suvorexant has a low potential for abuse relative to the drugs or other substances in schedule III. Suvorexant was compared to zolpidem in human studies of recreational sedative users to measure its abuse potential relative to that of a sedative-hypnotic in schedule IV. The abuse potential of suvorexant (40, 80 and 150 mg) relative to zolpidem (15 and 30 mg) and placebo was evaluated via a visual analog scale VAS, with results demonstrating that the effects of suvorexant were statistically indistinguishable from zolpidem. The results of the human abuse potential study suggest that suvorexant and zolpidem produce similar reinforcing effects and have a similar potential for abuse. In addition, preclinical

studies demonstrated that suvorexant (10, 20, 30 and 60 mg/kg) dose dependently reduced locomotor activity in rats, similar to other sedative drugs including zolpidem (schedule IV). Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that suvorexant has an abuse potential similar to other schedule IV drugs, including zolpidem (schedule IV).

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and the DEA's consideration of its eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of suvorexant. As such, the scheduling suvorexant 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 CSA outlines the findings required for placing 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 the HHS and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

(1) [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) has a low potential for abuse relative to the drugs or other substances in schedule III. The overall abuse potential of suvorexant is comparable to the schedule IV controlled substance zolpidem;

(2) [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) has a currently accepted medical use in treatment in the United States. Suvorexant was approved for marketing by FDA as a treatment for insomnia; and

(3) Abuse of [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III. The potential for psychological dependence is similar to that of zolpidem (schedule IV).

Based on these findings, the Deputy Administrator of the DEA concludes that suvorexant, including its salts, isomers, and salts of isomers, warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Suvorexant

Upon the effective date of this final rule, any person who handles suvorexant is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement in research, and conduct of instructional activities, of schedule IV controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) suvorexant, or who desires to handle suvorexant, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of September 29, 2014. Any person who currently handles suvorexant and is not registered with the DEA must submit an application for registration and may not continue to handle suvorexant as of September 29, 2014 unless the DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Security. Suvorexant is subject to schedule III-V security requirements and must be handled and stored pursuant to **21 U.S.C. 821**, **823**, and **871**(b) and in accordance with **21 CFR 1301.71**-**1301.93**, as of September 29, 2014.

Labeling and Packaging. All labels, labeling, and packaging for commercial containers of suvorexant must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302**, as of September 29, 2014.

Inventory. Every DEA registrant who possesses any quantity of suvorexant on the effective date of this final rule must take an inventory of all stocks of suvorexant on hand as of September 29, 2014, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d).

Any person who becomes registered with the DEA after September 29, 2014

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must take an initial inventory of all stocks of controlled substances (including suvorexant) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958** and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b).

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including suvorexant) on hand every two years, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records. All DEA registrants must maintain records with respect to suvorexant pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304**, **1307**, and **1312**, as of September 29, 2014.

Prescriptions. All prescriptions for suvorexant or products containing suvorexant must comply with **21 U.S.C. 829**, and be issued in accordance with **21 CFR part 1306** and subpart C of **21 CFR part 1311** as of September 29, 2014.

Importation and Exportation. All importation and exportation of suvorexant must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and be in accordance with **21 CFR part 1312** as of September 29, 2014.

Liability. Any activity involving suvorexant not authorized by, or in violation of, the CSA, occurring as of September 29, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal proceedings.

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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

This rule does not have tribal implications warranting the application of Executive Order 13175. The rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601-612, has reviewed this final rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this final rule is to place suvorexant, including its salts, isomers, and salts of isomers, into schedule IV of the CSA. No less restrictive measures (i.e., non-control, or control in schedule V) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Suvorexant is a new molecular entity which has not yet been marketed in the United States or any other country. Accordingly, the number of currently identifiable manufacturers, importers, and distributors for suvorexant is extremely small. The publicly available materials also specify the readily identifiable persons subject to direct regulation by this final rule. Based on guidelines utilized by the Small Business Administration (SBA), the suvorexant manufacturer/ distributor/importer was determined not to be a small entity. Once generic equivalents of suvorexant are developed and approved for manufacturing and marketing, there may be additional manufacturers, importers, and distributors of suvorexant, but whether they may qualify as small entities cannot be determined at this time.

There are approximately 1.5 million controlled substance registrations that represent approximately 381,000 entities (which include businesses, organizations, and governmental jurisdictions). The DEA estimates that 371,000 (97%) of these entities are considered "small entities" in accordance with the RFA and SBA size standards. 5 U.S.C. 601(6); 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the dispensing rates of new molecular entities, the DEA is unable to determine what number of these 371,000 small entities might handle suvorexant.

Despite the fact that the number of small entities possibly impacted by this rule could not be determined, the DEA concludes that they would not experience a significant economic impact as a result of this final rule. The DEA estimates all anticipated suvorexant handlers to be DEA registrants and currently 98% of DEA registrants (most of which are small entities) are authorized to handle schedule IV controlled substances. Registrants that handle suvorexant are expected to incur nominal additional security, inventory, and recordkeeping costs. These registered entities are likely to have already established and implemented the systems and processes required to handle schedule IV controlled substances and can easily absorb the costs of handling suvorexant with nominal to no additional economic burden. For example, because DEA-registered pharmacies and institutional practitioners are likely to already be schedule IV handlers, they may secure schedule II-V controlled substances by dispersing such substances throughout the stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances. Additionally, because other DEA registrants who will handle suvorexant are likely to already be schedule IV handlers, they already should have existing secure storage areas for schedule II-V controlled substances, which we assume would be able to accommodate any new stocks of suvorexant. See **21 CFR 1301.75** (b), **1301.72**(b). Accordingly, the requirement to secure all controlled substances containing suvorexant would not impose a significant economic burden upon DEA-registered practitioners as the infrastructure and materials for doing so are already in place. The DEA therefore assumes that the cost of compliance with **21 CFR 1301.71-1301.77** as a result of this final rule is nominal.

Correspondingly, because DEA-registered manufacturers, distributors,

[[Page 51247]]

and importers must label and package all schedule II-V controlled substances in accordance with **21 CFR part 1302**, the requirement to label and package all controlled substances containing suvorexant in accordance with 21 CFR part 1302 would not impose a significant economic burden upon DEA-registered manufacturers, distributors, and importers as the infrastructure and materials for doing so would already be in place. Accordingly, compliance with 21 CFR part 1302 would not require significant additional manpower, capital investment, or recordkeeping burdens.

Because of these facts, this final rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year . . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA 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. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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, the DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

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

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

- 2. Amend **Sec. 1308.14** by redesignating paragraphs (c)(49) through (c)(54) as (c)(50) through (c)(55) and adding new paragraph (c)(49) to read as follows:

Sec. 1308.14 Schedule IV.

* * * * *

(c) * * *

(49) Suvorexant 2223

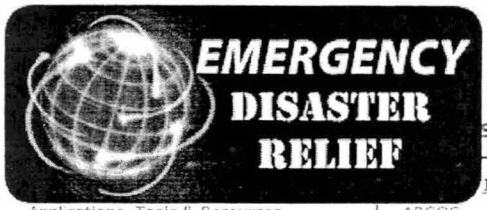
* * * * *

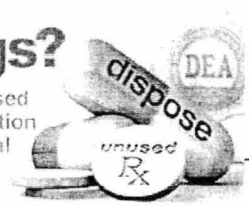
Dated: August 21, 2014.

Thomas M. Harrigan,
Deputy Administrator.

[FR Doc. 2014-20515 Filed 8-27-14; 8:45 am]

BILLING CODE 4410-09-P





Applications, Tools & Resources
CMEA Required Training & Self-Certification
Quota Applications

ABOUT US

Program Description
Customer Service Plan
DEA Forms & Applications
Mailing Addresses
Meetings & Events
What's New

ARCOS
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Import/Export
Inventory of Drugs Surrendered
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Reports Required by 21 CFR
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Year-End Reports

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Chemical Control Program
CMEA (Combat Meth Epidemic Act)
Controlled Substance Schedules
DATA Waived Physicians
Drug Disposal Information
Drug and Chemical Information
E-commerce Initiatives
Federal Agencies & Related Links
Federal Register Notices

National Take-Back Initiative
NFLIS
Publications & Manuals
Questions & Answers
Significant Guidance Documents
Title 21 Code of Federal Regulations
Title 21 USC Codified CSA

OFFICE OF DIVERSION CONTROL

U.S. DEPARTMENT OF JUSTICE • DRUG ENFORCEMENT ADMINISTRATION
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SB 2100

#3-1

Charlene Keller
Forensic Scientist
January 14, 2015

The designer drug market is still changing and new substances are still being created to evade legislation previously passed, but not nearly to the scale that we were dealing with a few years ago. Last legislative session I told you about the three main groups of designer drugs: Synthetic Cannabinoids – sold as incense or potpourri giving users a high similar to THC (Marijuana), Substituted Cathinones – sold as Bath Salts producing central nervous system stimulant effects, and Hallucinogens – producing effects similar to LSD. Legislation was passed for each of these groups using a chemical class approach which defined a core molecular structure and listed possible substitutions and modifications. These laws have helped in the fight against designer drugs as a large number of compounds and their derivatives are controlled in our state, and we have noticed a large decrease in the amount being submitted to the ND Crime Lab. The good news is our current laws for the Substituted Cathinones (Bath Salts) and Hallucinogens is sufficient, and no changes or additions need to be made at this time. DEA has recently specifically listed some of these compounds into the federal code but these were already included in our state law (along with their listed derivatives). This shows that our approach is working and is proactive. The synthetic cannabinoids group is where some changes are required, as new derivatives continue to show up that are not included in our current legislation. The number of synthetic cannabinoid samples submitted to lab has greatly decreased. But when a synthetic cannabinoid sample is identified, there is a good chance it is no longer one of the previously controlled compounds but rather one belonging to a new generation of synthetic cannabinoid compounds.

This session, the proposed changes include adding three new groups under the synthetic cannabinoid section. These group definitions are more comprehensive and therefore would replace four of the existing cannabinoid groups. The first new group, Indole Carboxaldehydes, replaces the following current groups in the century code: Naphthoylindoles, Phenylacetylindoles, Benzoylindoles, and Tetramethylcyclopropanoylindoles. The definition includes all of the compounds in the four replaced groups and additionally includes compounds not covered in the previous definitions. The other two new groups would include newer compounds the forensic community has identified in casework and would include a few of the compounds that were currently listed in the 'others specifically named' section. To summarize, currently there are eight defined cannabinoid groups with nine compounds listed specifically. With the proposed changes, the new legislation would have seven cannabinoid groups with four compounds specifically named. The three new defined core structure groups with listed substitutions is more comprehensive and includes more compounds, including the new generation of compounds identified in forensic case work.

North Dakota has some of the best all inclusive laws encompassing hundreds of compounds when you compare our law to some other states. The laws specifically define what is and what is not covered in the definitions of the groups and other states have followed our lead with some of the definitions. It may seem like it is a never ending battle with designer drugs, but all we can do is to stay on top of what is currently being identified in the forensic community, and modify our laws accordingly. The laws are working and have made a difference. This session we are just proposing some fine tuning to the synthetic cannabinoid laws to make them more inclusive of past and present compounds.

1/20/2015 #1-1

15.8010.01002
Title.

Prepared by the Legislative Council staff for
Senator Anderson
January 14, 2015

PROPOSED AMENDMENTS TO SENATE BILL NO. 2100

Page 5, line 25, after the period insert "Other names: Delta-9-tetrahydrocannabinol."

Page 6, line 4, overstrike "Naphthoylindoles. Any compound containing a 3-(1-naphthoyl)indole"

Page 6, overstrike lines 5 through 22

Page 6, line 23, remove "(1)"

Page 6, line 31, replace "by: a substitution" with "in the following ways:

(a) Substitution"

Page 7, line 1, replace "a substitution" with "or

(b) Substitution"

Page 7, line 2, after the second underscored comma insert "or"

Page 7, line 2, replace "A" with "or

(c) A"

Page 7, after line 3, insert:

"(d)"

Page 7, after line 4, insert:

"(e)"

Page 7, line 6, replace "~~[1]~~(a)" with "[1]"

Page 7, line 7, replace "~~[2]~~(b)" with "[2]"

Page 7, line 8, replace "~~[3]~~(c)" with "[3]"

Page 7, line 9, replace "~~[4]~~(d)" with "[4]"

Page 7, line 11, replace "~~[5]~~(e)" with "[5]"

Page 7, line 12, replace "~~[6]~~(f)" with "[6]"

Page 7, line 13, replace "~~[7]~~(g)" with "[7]"

Page 7, line 14, replace "~~[8]~~(h)" with "[8]"

Page 7, line 15, replace "~~[9]~~(i)" with "[9]"

Page 7, line 16, replace "~~[10]~~(j)" with "[10]"

Page 7, line 17, replace "~~[11]~~(k)" with "[11]"

Page 7, line 19, replace "~~[12]~~(l)" with "[12]"

Page 7, line 20, replace "~~[13]~~(m)" with "[13]"

Page 7, line 21, replace "~~[14]~~(n)" with "[14]"

#1-2

Page 7, line 22, replace "~~[15]~~(o)" with "[15]"

Page 7, line 23, replace "~~[16]~~(p)" with "[16]"

Page 7, line 24, replace "~~[17]~~(q)" with "[17]"

Page 7, line 26, replace "~~[18]~~(r)" with "[18]"

Page 7, line 28, replace "~~[19]~~(s)" with "[19]"

Page 7, line 30, replace "~~[20]~~(t)" with "[20]"

Page 8, line 1, replace "~~[21]~~(u)" with "[21]"

Page 8, line 3, replace "~~[22]~~(v)" with "[22]"

Page 8, line 5, replace "~~[23]~~(w)" with "[23]"

Page 8, after line 6, insert:

"[24] 1-[(N-methylpiperidin-2-yl)methyl]-3-(adamant-1-oyl)indole - Other names: AM-1248.

[25] 1-Pentyl-3-(1-adamantoyl)indole - Other names: AB-001 and JWH-018 adamantyl analog."

Page 8, line 15, replace "by: a substitution" with "in the following ways:

(a) Subsitution"

Page 8, line 16, replace "a substitution" with: "or

(b) Substitution"

Page 8, line 17, replace "a" with "or

"(c) A"

Page 8, line 18, replace the first underscored comma with an underscored semicolon

Page 8, line 18, replace "a" with:

"(d) A"

Page 8, after line 19, insert:

"(e) "

Page 8, remove lines 20 and 21

Page 8, line 22, replace "(b)" with "[1]"

Page 8, line 23, after "carboxamide" insert ", APICA, SDB-001, and 2NE1

Page 8, line 24, replace "(c)" with "[2]"

Page 8, line 26, replace "(d)" with "[3]"

Page 8, line 27, after "48" insert "and APINACA"

Page 8, removes lines 28 through 31

Page 9, line 1, replace "(g)" with "[4]"

#1-3

Page 9, line 3, replace "(h)" with "[5]"

Page 9, line 5, replace "(i)" with "[6]"

Page 9, line 7, replace "(j)" with "[7]"

Page 9, line 9, replace "(k)" with "[8]"

Page 9, line 11, replace "(l)" with "[9]"

Page 9, line 13, replace "(m)" with "[10]"

Page 9, line 15, replace "(n)" with "[11]"

Page 9, line 17, replace "(o)" with "[12]"

Page 9, line 20, replace "(p)" with "[13]"

Page 9, line 22, replace "(q)" with "[14]"

Page 9, line 24, replace "(r)" with "[15]"

Page 10, line 3, replace "by: a substitution" with "in the following ways:

(a) Substitution"

Page 10, line 4, replace "a substitution" with "or

(b) Substitution"

Page 10, line 5, replace "a" with "or

(c) A"

Page 10, line 6, replace "a" with:

"(d) A"

Page 10, after line 7, insert:

"(e) "

Page 10, line 9, replace "(a)" with "[1]"

Page 10, line 11, replace "(b)" with "[2]"

Page 10, line 13, replace "(c)" with "[3]"

Page 10, line 15, replace "(d)" with "[4]"

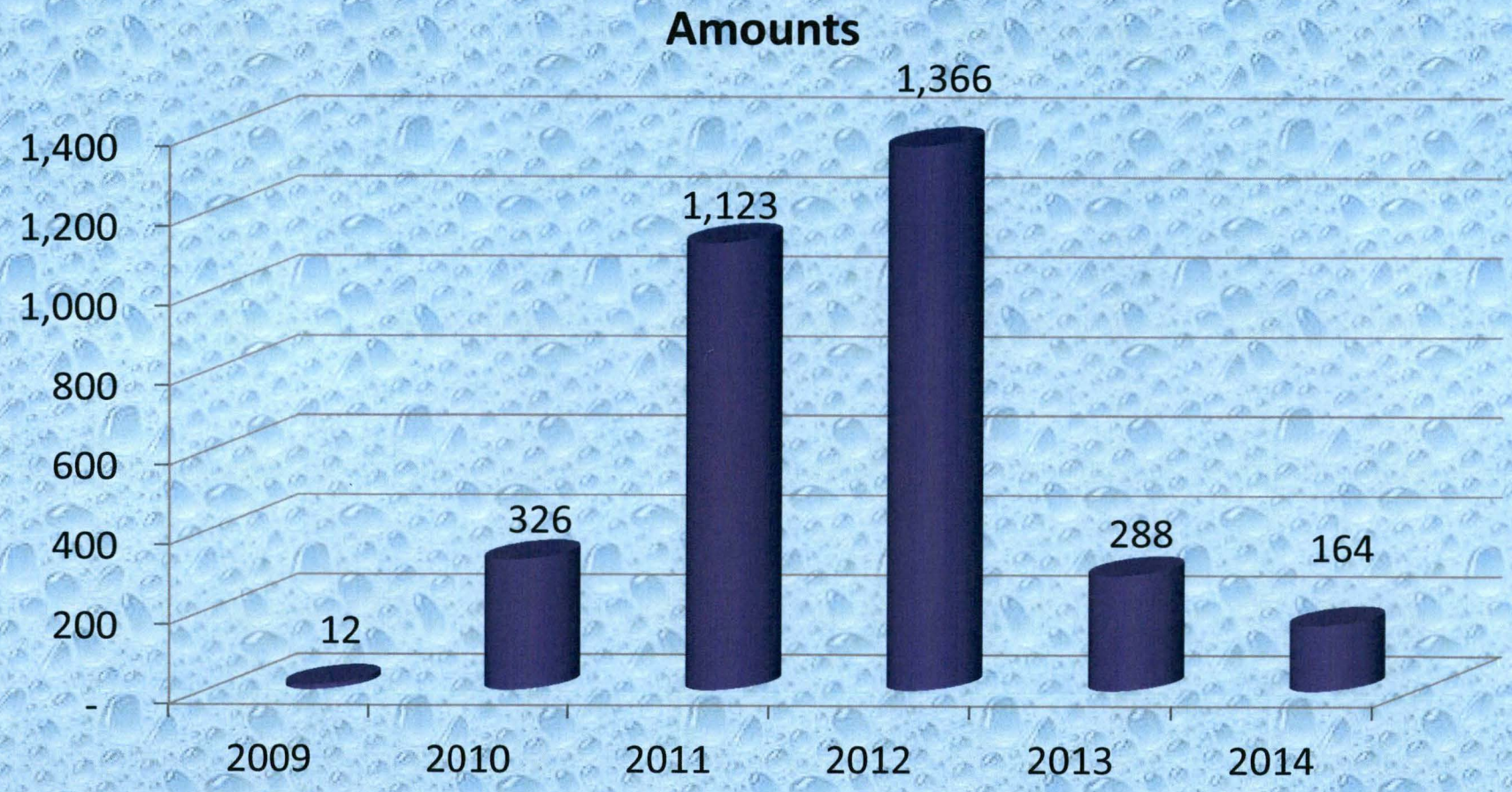
Page 10, line 17, replace "(e)" with "[5]"

Page 10, line 19, replace "(f)" with "[6]"

Page 27, line 4, underscore "Alfaxalone"

Renumber accordingly

SYNTHETIC DRUG CASES (THROUGH NOVEMBER 2014)



A.G. 1/20/2015 # 2-1

#1

State of North Dakota
Jack Dalrynple, Governor

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Mark J. Hardy, PharmD, R.Ph.
Executive Director

Senate Bill No 2100 – Controlled Substances Rescheduling
House Human Services Committee – Fort Union Room
9:00 AM - Tuesday – March 10, 2015

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

Senate Bill 2100 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 adds a few new categories for synthetic spice cannabinoids and compounds within Schedule I controlled substances. The drafting of this bill, specifically the Schedule I substances was done in conjunction with the North Dakota Crime Lab. A representative with the ND Crime Lab is here and will present testimony to explain much of the chemistry and reasons for the new categories listed in this proposed legislation. The intention for these changes is to try to be proactive and ensure that we have future chemical modifications that can be made to these substances, identified as controlled substances. This bill is very lengthy and, we feel, as comprehensive as possible with the information that we have at this time.

I would like to highlight each provision of the bill to ensure you have an understanding of the approach and specific addition we made in the drafting of this bill.

On page one, line 18 we have added Acetylfentanyl as a Schedule I substance, which the state crime lab and federal authorities have identified as a drug of concern.

On page 5 lines 25 & 26 an addition of Delta-9-tetrahydrocannabinol was added as it is a common name for the compound listed. This was recommended by the ND State Crime Lab.

Starting on page 6 are the new categories for synthetic spice cannabinoids and compounds, which are inclusive of the current cannabinoids listed in the current code. We have moved all specific compounds identified by the state crime lab under the applicable section, to make it clear for those prosecuting or identifying those specific compounds.

/

It may appear there are many lines struck under the current legislation, but please be aware that each individual compound was moved to the specific applicable new section.

Again, this is a strategy to be proactive in the complex nature of modifying these dangerous drugs to circumvent legislation and to try to keep these dangerous substances away from our citizens.

As I indicated earlier, a representative with the ND Crime Lab is here and will present testimony on these changes as they are the experts we rely upon to draft and refine this area of the law.

On page 22, line 15 there is the addition of Perampanel, which is a new controlled substance scheduled by DEA since our last legislative session.

On page 23, lines 4-9, you will notice the provisions of hydrocodone being struck from this section and moved to Schedule II. DEA has recently lifted the provisions of exemptions for those hydrocodone compounds in schedule III. Hydrocodone products are commonly referred to as Vicodin, Loracet and Norco. They are a drug that is commonly abused.

On page 27, line 25 the addition of Alfaxalone was made as done by the DEA. Alfaxalone is another compound that DEA scheduled.

On page 29, line 12 Suvorexant is also a new drug that fell under schedule IV.

We have requested an emergency clause on this measure to ensure it is effective as soon as possible.

Again, thank you for your time. I will be glad to answer any questions you have at this time.

U.S. Department of Justice
Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

SB2100
3-10-15
1b

Lists of:

Scheduling Actions
Controlled Substances
Regulated Chemicals

September 2014

SUBSTANCE *Scheduled under 21 USC 811(h) **Extension of temporary control	PROPOSAL PUBLICATION DATE	FINAL ORDER PUBLICATION DATE	FEDERAL REGISTER CITATION	EFFECTIVE DATE	CSA SCHEDULE
JWH-200 **		02-29-12	77 FR 12201	2/29/2012	I
METHASTERONE (2 ALPHA-17 ALPHA-DIMETHYL-5 ALPHA-ANDROSTAN-17BETA-OL-3-ONE)	11-23-11	07-30-12	77 FR 44456	8/29/2012	III
PROSTANOZOL (17 BETA-HYDROXY-5 ALPHA-ANDROSTANO[3,2-C]PRYAZOLE	11-23-11	07-30-12	77 FR 44456	8/29/2012	III
3,4-METHYLENEDIOXY-N-METHYLCATHINONE (METHYLONE)	10-21-11	04-12-13	78 FR 21818	4/12/2013	I
[1-(5-FLUORO-PENTYL)1H-INDOL-3-YL](2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE(5-FLOURO-UR-144, XLR11)*		05-16-13	78 FR 28735	5/16/2013	I
(1-PENTYL-1H-INDOL-3-YL)(2,2,3,3-TETRAMETHYLCYCLOPROPYL)METHANONE (UR-144)*		05-16-13	78 FR 28735	5/16/2013	I
N-(1-ADAMANTYL)-1-PENTYL-1H-INDAZOLE-3-CARBOXAMIDE (APINACA, AKB48)*		05-16-13	78 FR 28735	5/16/2013	I
LORCASERIN	12-19-12	05-08-13	78 FR 26701	6/7/2013	IV
2-(4-CHLORO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25C-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
2-(4-IODO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25I-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
2-(4-BROMO-2,5-DIMETHOXYPHENYL)-N-(2-METHOXYBENZYL) ETHANAMINE (25B-NBOMe)*		11-15-13	78 FR 68716	11/15/2013	I
PERAMPANEL [2-(2-OXO-1-PHENYL-5-PYRIDIN-2-YL-I ,2-DIHYDROPYRIDIN-3-YL)BENZONITRILE]	10-22-13	12-02-13	78 FR 72013	1/2/2014	III
QUINOLIN-8-YL 1-PENTYL-1H-INDOLE-3-CARBOXYLATE (PB–22; QUPIC)*		02-10-14	79 FR 7577	2/10/2014	I
QUINOLIN-8-YL 1-(5-FLUOROPENTYL)-1H-INDOLE-3-CARBOXYLATE (5-FLUORO-PB–22; 5F–PB–22)*		02-10-14	79 FR 7577	2/10/2014	I
N-(1-AMINO-3-METHYL-1-OXOBUTAN-2-YL)-1-(4-FLUOROBENZYL)-1H-INDAZOLE-3-CARBOXAMIDE (AB-FUBINACA)*		02-10-14	79 FR 7577	2/10/2014	I
N-(1-AMINO-3,3-DIMETHYL-1-OXOBUTAN-2-YL)-1-PENTYL-1H-INDAZOLE-3-CARBOXAMIDE (ADB-PINACA)*		02-10-14	79 FR 7577	2/10/2014	I
ALPHA-PYRROLIDINOBUTIOPHENONE (α-PBP)*		03-07-14	79 FR 12928	3/7/2014	I
3-FLUORO-N-METHYLCATHINONE (3-FMC)*		03-07-14	79 FR 12928	3/7/2014	I
4-FLUORO-N-METHYLCATHINONE (4-FMC)*		03-07-14	79 FR 12928	3/7/2014	I
4-METHYL-N-ETHYLCATHINONE (4-MEC)*		03-07-14	79 FR 12928	3/7/2014	I
PENTYLONE*		03-07-14	79 FR 12928	3/7/2014	I
ALPHA-PYRROLIDINOPENTIOPHENONE (α-PVP)*		03-07-14	79 FR 12928	3/7/2014	I
BUTYLONE*		03-07-14	79 FR 12928	3/7/2014	I
NAPHYRONE*		03-07-14	79 FR 12928	3/7/2014	I
4-METHYL-ALPHAPYRROLIDINOPROPIOPHENONE (4-MePPP)*		03-07-14	79 FR 12928	3/7/2014	I
PENTEDRONE*		03-07-14	79 FR 12938	3/7/2014	I
ALFAXALONE (5α-PREGNAN-3α-OL-11,20-DIONE)	03-25-13	02-27-14	79 FR 10985	3/31/2014	IV
TRAMADOL (2-[(DIMETHYLAMINO)METHYL]-1-(3-METHOXYPHENYL)CYCLOHEXANOL)	11-04-13	07-02-14	79 FR 37623	8/18/2014	IV

SUBSTANCE *Scheduled under 21 USC 811(h) **Extension of temporary control	PROPOSAL PUBLICATION DATE	FINAL ORDER			
		PUBLICATION DATE	FEDERAL REGISTER CITATION	EFFECTIVE DATE	CSA SCHEDULE
SUVOREXANT	02-13-14	08-28-14	79 FR 52143	9/29/2014	IV
HYDROCODONE COMBINATION PRODUCTS	02-27-14	08-22-14	79 FR 49661	10/6/2014	III->II

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

Acetylfentanyl
(*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide)

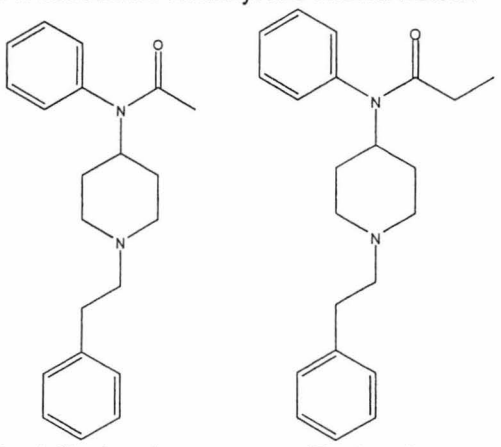
December 2013
DEA/OD/ODE

Introduction:

Acetylfentanyl, similar to the Schedule II opioid fentanyl, is a potent opioid analgesic. Recently, it has been linked to a number of overdose deaths in the northeastern part of the U.S. Acetylfentanyl is not a part of most illicit drug screens and remained undetected in many of these cases. Upon being identified in one death, secondary analyses were performed to confirm the presence of acetylfentanyl in numerous jurisdictions.

Chemistry:

The chemical structure of acetylfentanyl and the Schedule II substance fentanyl are shown below.



Acetylfentanyl Fentanyl

Acetylfentanyl and fentanyl are both synthetic opioids and have similar structures. With one less methyl group attached to the amide group, acetylfentanyl is the N-acetyl version of fentanyl.

Pharmacology:

Acetylfentanyl (EC_{50} = 676 nM), similar to morphine (EC_{50} = 23.6 nM), has been shown to bind to μ-opioid receptors in rat cerebrum membrane preparations. Acetylfentanyl, similar to morphine, has been shown to inhibit the twitch response in electrically stimulated vas deferens preparation. A pharmacology study using acetic acid writhing test showed that acetylfentanyl produces analgesic response in mice 15.7-fold more potent than that of morphine. Potency of acetylfentanyl was about 3-fold less than that of fentanyl in this assay. The ED_{50} (the dose at which 50% of test animals had met the criterion for analgesic response) dose for acetylfentanyl, fentanyl and morphine were 0.021, 0.0061, and 0.33 mg/kg, respectively. Similarly, in another study using tail flick and phenylquinone writhing tests, acetylfentanyl produced analgesic response in mice. Acetylfentanyl has been shown to completely suppress the signs of withdrawal in morphine-dependent monkeys.

Besides analgesia, fentanyl-like substances, similar to other opioid analgesics, produce a variety of pharmacological effects including alteration in mood, euphoria, drowsiness, respiratory depression, suppression of cough reflex, constriction of pupils (miosis), and impaired gastrointestinal motility. Clinical studies evaluating pharmacological effects of acetylfentanyl in humans have not been reported in the scientific literature.

In acute toxicity studies in mice, the LD_{50} (the dose causing death of 50% of test animals) of acetylfentanyl and fentanyl are 9.3 mg/kg and 62 mg/kg, respectively. Significant bleeding in the small intestines of mice was observed in acetylfentanyl-administered mice.

Licit Uses:

There are no published studies as to the safety of acetylfentanyl for human use. There are no commercial medical uses for this substance.

Illicit Uses:

As a μ-opioid receptor agonist, acetylfentanyl may serve as a direct substitute for heroin or other μ-opioid receptor agonist substances in opioid dependent individuals.

Recently, the Centers for Disease Control and Prevention (CDC) issued a health alert to report that between March 2013 and May 2013, 14 overdose deaths related to injected acetylfentanyl had occurred among intravenous drug users (ages between 19 and 57 years) in Rhode Island.

After confirming five overdoses in one county, including a fatality, Pennsylvania asked coroners and medical examiners across the state to screen for acetylfentanyl. This request led to 50 confirmed fatalities and five non-fatal overdoses statewide in 2013.

Control Status

Acetylfentanyl is not currently scheduled under the Controlled Substance Act (CSA). However, if intended for human consumption, acetylfentanyl may be treated as a "controlled substance analogue" under the CSA pursuant to 21 U.S.C §§802(32)(A) and 813.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 202-353-1263, telephone 202-307-7183, or E-mail ODE@usdoj.gov.

Rules - 2013

[Federal Register Volume 78, Number 231 (Monday, December 2, 2013)]
[Rules and Regulations]
[Pages 72013-72016]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2013-28778]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-374]

Schedules of Controlled Substances: Placement of Perampanel into Schedule III

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Deputy Administrator of the Drug Enforcement Administration (DEA) places the substance perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile], including its salts, isomers, and salts of isomers, into schedule III of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule III controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, or possess) or propose to handle perampanel.

DATES: Effective Date: January 2, 2014.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Chief, Policy Evaluation and Analysis Section, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, but they are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purposes of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in **title 21 of the Code of Federal Regulations (CFR) parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

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 established by Congress 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 **[21 U.S.C. 812**(b)] 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 the DEA, who has further delegated this authority to the Deputy Administrator of the DEA. 28 CFR 0.104.

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 the Department of Health and Human Services (HHS),\1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action is based on a recommendation from the Assistant Secretary of the HHS and on an evaluation of all other relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule III controlled substances on persons who handle or propose to handle perampanel.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1995. In addition, because the Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations, for purposes of this document, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

Background

Perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3- yl) benzonitrile] is a new chemical entity with central nervous system (CNS)

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depressant and hallucinogenic properties. On October 22, 2012, the Food and Drug Administration (FDA) approved a new drug application for perampanel as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel will be marketed in the United States under the trade name FYCOMPA[supreg]. Perampanel is a non-competitive AMPA ([alpha]-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid)-type glutamate receptor antagonist. Perampanel was approved in Europe in May 2012 and has been marketed there since July 2012.

HHS and DEA Eight-Factor Analyses

On January 22, 2013, the Assistant Secretary of the HHS provided to the DEA a scientific and medical evaluation and scheduling recommendation entitled "Basis fo the Recommendation for Control of Perampanel and its Salts in Schedule III of the Controlled Substances Act." Following consideration of the eight factors and fin related to the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that perampanel be controlled in schedule III of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eight-factor analysis of perampanel pursuant to **21 U.S.C. 811** (c). Electronic copies of these documents are available at www.regulations.gov for easy reference.

Determination to Schedule Perampanel

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Deputy Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Perampanel into Schedule III" on October 22, 2013 (78 FR 62500), which proposed placement of perampanel in schedule III of the CSA. The NPRM provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations on or before November 21, 2013. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposed rule on or before November 21, 2013.

Comments Received

The DEA received two comments on the proposed rule to schedule perampanel. One commenter was in favor of controlling perampanel as a schedule III controlled substance. Another commenter requested that the DEA make the rule effective on the same date as the publication of the final rule.

Support for the Proposed Rule: One commenter supported controlling perampanel as a schedule III controlled substance, as opposed to a schedule II controlled substance, but expressed concern about the unknown effects and abuse potential of this new drug at higher doses. However, the commenter indicated that the controls applicable to schedule III controlled substances are appropriate until there is more available data on perampanel's effects.

DEA Response: The DEA appreciates the comment in support of this rulemaking.

Request to Change Effective Date: One commenter requested that the DEA make this rule effective on the same date as publication to enable physicians and their patients to have access to perampanel as soon as possible and pointed out that the DEA has included an earlier effective date in the final rule for other drugs including zopiclone, pregablin, and ezogabine.

DEA Response: The DEA appreciates the commenter's request, but does not believe an earlier effective date is warranted. As provided in **21 CFR 1308.45**, final orders shall not have an effective date of "less than 30 days from the date of publication in the Federal Register unless the Administrator finds that the conditions of public health or safety necessitate an earlier effective date . . . ." The Administrator finds that the conditions of public health or safety do not necessitate such an earlier effective date in this instance. There are other anti-seizure medications currently available, specifically lacosamide, an anti-epileptic medication that has a similar clinical indication to perampanel. Though the mechanisms of actions of perampanel and lacosamide are different, the indications are very similar. Like perampanel, lacosamide is indicated as an adjunctive therapy for the treatment of partial-onset seizures, and did not have its 30-day implementation period waived. Furthermore, the DEA believes that providing 30 days for this Final Rule to become effective is expeditious and sufficient to allow handlers to obtain the appropriate registration with the DEA and to comply with regulatory requirements for handling schedule III controlled substances.

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of perampanel. As such, the DEA is scheduling perampanel 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 for placing a drug o 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 the HHS and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(3), finds that:

1. Perampanel has a potential for abuse less than the drugs or other substances in schedules I and II;
2. Perampanel has a currently accepted medical use in treatment in the United States. Perampanel was approved for marketing by the FDA as an adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older; and
3. Abuse of perampanel may lead to moderate or low physical dependence or high psychological dependence.

Based on these findings, the Deputy Administrator of the DEA concludes that perampanel, including its salts, isomers, and salts of isomers, warrants control in schedule III of the CSA. **21 U.S.C. 812**(b)(3).

Requirements for Handling Perampanel

Upon the effective date of this final rule, any person who handles perampanel is subject to the CSA's schedule III regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement of research, and conduct of instructional activities, of schedule III controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) perampanel, or who desires to handle perampanel, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of January 2, 2014. Any person who is currently engaged in any of the above activities and is not registered with the DEA must

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submit an application for registration and may not continue their activities as of January 2, 2014 unless the DEA has approved that application, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312**.

Security. Perampanel is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93**, pursuant to **21 U.S.C. 823**, **821**, **871**(b) as of January 2, 2014.

Labeling and Packaging. All labels and labeling for commercial containers of perampanel must be in accordance with **21 CFR 1302.03-1302.07**, pursuant to **21 U.S.C. 825**, **958**(e) as of January 2, 2014.

Inventory. Every DEA registrant who possesses any quantity of perampanel on the effective date of this final rule is required to take an inventory of all stocks of perampanel on hand as of January 2, 2014, pursuant to **21 U.S.C. 827**, **958**(e), and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d). Any person who becomes registered with the DEA after January 2, 2014 is required to take an initial inventory of all controlled substances (including perampanel) on hand at the time of registration, pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b). After the initial inventory every DEA registrant is required to take a biennial inventory of all controlled substances (including perampanel), on hand pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR 1304.03, 1304.04 and 1304.11.

Records. All DEA registrants must keep records with respect to perampanel pursuant to **21 U.S.C. 827**, **958**(e) and in accordance with **21 CFR parts 1304**, **130** and **1312**, as of January 2, 2014.

Prescriptions. All prescriptions for perampanel or prescriptions for products containing perampanel must comply with **21 U.S.C. 829** and must be issued in accordance with **21 CFR part 1306** as of January 2, 2014.

Importation and Exportation. All importation and exportation of perampanel must be done in accordance with **21 CFR part 1312**, pursuant to **21 U.S.C. 952**, **953**, **957**, and **958** as of January 2, 2014.

Criminal Liability. Any activity involving perampanel not authorized by, or in violation of, the CSA, occurring as of January 2, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

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 performed "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 procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) 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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612), has reviewed this rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to place perampanel, including its salts, isomers, and salts of isomers, into schedule III of the CSA. No less restrictive measures (i.e., non-control or control in a lower schedule) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Perampanel is a new molecular entity, approved by the FDA on October 22, 2012. It was approved in Europe in May 2012, and has been marketed in Europe since July 2012. According to publically available information reviewed by the DEA, perampanel is currently anticipated to enjoy patent protection for at least a decade before generic equivalents may be manufactured and marketed. Accordingly, the number of currently identifiable manufacturers, importers, and distributors for perampanel is extremely small. The publically available materials also specify the readily identifiable persons subject to direct regulation by this final rule. Based on guidelines utilized by the Small Business Administration (SBA), the perampanel manufacturer/ distributor/importer was determined not to be a small entity. Once generic equivalents are developed and approved for manufacturing and marketing, there may be additional manufacturers, importers, and distributors of perampanel, but whether they may qualify as small entities cannot be determined at this time.

There are approximately 1.5 million controlled substance registrants, who represent approximately 381,000 entities. The DEA estimates that 371,000 (97 percent) of these businesses are considered "small entities" in accordance with the RFA and SBA standards. 5 U.S.C. 601(6) and 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that could potentially influence the dispensing rates of new chemical entities, the DEA is unable to determine the number of small entities that might dispense (including administer and prescribe) perampanel (e.g., pharmacies and prescribers).

Despite the fact that the number of small businesses potentially impacted by this final rule could not be determined at this time, the DEA concludes that they would not experience a significant economic impact as a result of this rule. The DEA estimates all anticipated perampanel handlers to be DEA registrants and currently 98 percent of DEA registrants (most of which are small businesses) are authorized to handle schedule III controlled substances. Even if we assume that all of the DEA registrants were to dispense perampanel, (e.g., practitioners prescribe, administer, or dispense the substance, and pharmacies dispense the prescriptions), the costs that they would incur as a result of perampanel scheduling would be

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minimal. Registrants that dispense (but not prescribe) would incur nominal additional security, inventory, recordkeeping, and labeling costs, as they have already established and implemented the required systems and processes to handle schedule III controlled substances. For example, pharmacies and institutional practitioners may disperse schedule II-V controlled substances throughout their stock of non- controlled substances in such a manner as to obstruct theft or diversion of the controlled substances. The inclusion of one additional substance to this system would result in little or no additional burden to such practitioners. In addition, because DEA-registered dispensers must label all schedule II-V controlled substances dispensed, the requirement to label all controlled substances containing perampanel would not impose a significant economic burden upon DEA-registered dispensers (as the infrastructure and materials for doing so would already be in place). Accordingly, compliance would not require significant manpower, capital investments, or recordkeeping burdens.

Registrants who only prescribe perampanel by oral or written prescription would not incur any additional security, inventory, recordkeeping, or labeling costs as a result of this rule, as they would not physically handle perampanel.

Because of these facts, this rule will not result in significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), on the basis of information contained in the "Regulatory Flexibility Act" section above, the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year . . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA 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). This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 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.

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- 2. Amend **Sec. 1308.13** by redesignating paragraphs (c)(11) through (c)(14) as paragraphs (c)(12) through (c)(15) and adding new paragraph (c)(11) to read as follows:

Sec. 1308.13 Schedule III.

* * * * *

(c) * * *

(11) Perampanel, and its salts, isomers, and salts of isomers.. 2261

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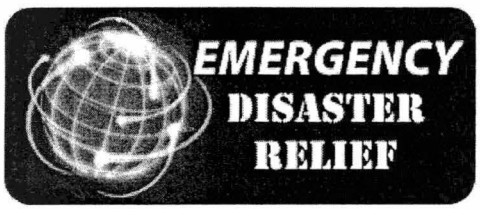
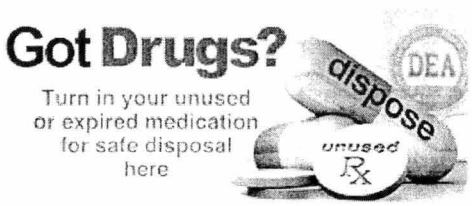
Dated: November 25, 2013.

Thomas M. Harrigan,
Deputy Administrator.

[FR Doc. 2013-28778 Filed 11-29-13; 8:45 am]

BILLING CODE 4410-09-P





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Rules - 2014

[Federal Register Volume 79, Number 163 (Friday, August 22, 2014)]
[Rules and Regulations]
[Pages 49661-49682]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014-19922]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-389]

Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II

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 reschedules hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule II controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, conduct chemical analysis with, or possess) or propose to handle hydrocodone combination products.

DATES: This rule is effective October 6, 2014.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, Telephone: (202) 598- 6812.

SUPPLEMENTARY INFORMATION:

Outline

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I. Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referre as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substa Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, every controlled substance is classified into one of five schedules based upon its potential for abuse, currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause. **21 U.S.C. 812**. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all scheduled substances is published at **21 CFR part 1308**. 21 U.S.C. 812(a).

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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." The Attorney General has delegated this scheduling authority to the Administrator of the DEA. 28 CFR 0.100(b).

The Administrator may initiate the scheduling of any drug or other substance (1) on her own motion; (2) at the request of the Secretary of the Department of Health and Human Services (HHS); or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action was initiated by a petition to reschedule hydrocodone combination products (HCPs) \1\ from schedule III to schedule II of the CSA, and is supported by, inter alia, a recommendation from the Assistant Secretary for Health of the HHS \2\ and an evaluation of all relevant data by the DEA. This final action imposes the regulatory controls and administrative, civil, and criminal sanctions of schedule II controlled substances on any person who handles, or proposes to handle, HCPs.

\1\ Hydrocodone combination products (HCPs) are pharmaceuticals containing specified doses of hydrocodone in combination with other drugs in specified amounts. These products are approved for marketing for the treatment of pain and for cough suppression.

\2\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

II. Background

Hydrocodone was listed in schedule II of the CSA upon the enactment of the CSA in 1971. Public Law 91-513, 84 Stat. 1236, sec. 202(c), schedule II, paragraph (a), clause (1) (codified at **21 U.S.C. 812**(c)); initially codified in DEA regulations at 21 CFR 308.12(b)(1)(x) (36 FR 7776, April 24, 1971) (currently codified at **21 CFR 1308.12**(b)(1)(vi)). At that time, hydrocodone was listed in schedule III of the CSA when formulated with specified amounts of an isoquinoline alkaloid of opium or one or more therapeutically active nonnarcotic ingredients. Pub. L. 91-513, 84 Stat. 1236, sec. 202(c), schedule III, paragraph (d), clauses (3) and (4) (codified at 21 U.S.C. 812(c)); initially codified at 21 CFR 308.13(e) (3) and (4) (36 FR 7776, April 24, 1971) (currently codified at **21 CFR 1308.13**(e)(1) (iii) and (iv)).\3\ Any other hydrocodone single-entity products or combinations of hydrocodone with other substances outside the range of specified doses are listed in schedule II of th CSA.\4\

\3\ Specifically: (iii) "Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with a fourfold or greater quantity of an isoquinoline alkaloid of opium;" (iv) "Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts"

\4\ In the United States there are currently no approved, marketed, products containing hydrocodone in combination with other active ingredients that fall outside schedule III of the CSA. Further, until recently, there were no approved hydrocodone single- entity schedule II products. In October 2013 the FDA approved Zohydro\TM\ ER, a single-entity, extended release schedule II product. Zohydro\TM\ ER was launched on March 3, 2014. Accordingly, all of the historical data regarding hydrocodone from different national and regional databases that support this rule should refer to HCPs only, regardless of whether the database utilizes the term "hydrocodone" or "hydrocodone combination products."

III. Determination To Transfer Hydrocodone Combination Products (HCPs) to Schedule II

Pursuant to **21 U.S.C. 811**(a), proceedings to add a drug or substance to those controlled under the CSA, or to transfer a drug between schedules, may be initiated on the petition of any interested party. The DEA received a petition requesting that HCPs be controlled in schedule II of the CSA. In response, in 2004, the DEA submitted a request to the HHS to provide the DEA with a scientific and medical evaluation of available information and a scheduling recommendation for HCPs, pursuant to 21 U.S.C. 811 (b) and (c). In 2008, the HHS provided to the DEA its recommendation that HCPs remain controlled in schedule III of the CSA. In response, in 2009, the DEA requested that the HHS re-evaluate their data and provide another scientific and medical evaluation and scheduling recommendation based on additional data and analysis.

On July 9, 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144, 126 Stat. 993) (FDASIA). Section 1139 of the FDASIA directed the Food and Drug Administration (FDA) to hold a public meeting to "solicit advice and recommendations" pertaining to the scientific and medical evaluation in connection with its scheduling recommendation to the DEA regarding drug products containing hydrocodone, combined with other analgesics or as an antitussive. Additionally, the Secretary was required to solicit stakeholder input "regarding the health benefits and risks, including the potential for abuse" of HCPs "and the impact of up-scheduling these products." Accordingly, on January 24 and 25, 2013, the FDA held a public Drug Safety and Risk Management Advisory Committee (DSaRM) meeting, at which the DEA made a presentation.\5\ The DSaRM Committee included members with scientific and medical expertise in the subject of opioid abuse, and a patient representative. Members included

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representatives from the National Institute on Drug Abuse (NIDA) and the Centers for Disease Control (CDC). There was also an opportunity for the public to provide comment. The DSaRM voted 19 to 10 in favor of recommending that HCPs be placed into schedule II. According to the FDA, 768 comments were submitted to the FDA by patients, patient groups, advocacy groups, and professional societies.

\5\ The DEA presentation is available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagmentadvisorycommittee/ucm346941.pdf.

Upon evaluating the scientific and medical evidence, along with the above considerations mandated by the FDASIA, the HHS on December 16, 2013, submitted to Administrator of the DEA its scientific and medical evaluation entitled, "Basis for the Recommendation to Place Hydrocodone Combination Products in Schedule II the Controlled Substances Act." Pursuant to **21 U.S.C. 811**(b), this document contained an eight-factor analysis of the abuse potential of HCPs, along with the HH recommendation to control HCPs in schedule II of the CSA.

The HHS stated that the comments received during the open public hearing and submitted to the docket, and the discussion of the DSaRM members of the FDA DSaRM meeting provided support for its conclusion that: (1) Individuals are taking HCPs in amounts sufficient to create a hazard to their health or to the safety of

other individuals or to the community; (2) there is significant diversion of HCPs; and (3) individuals are taking HCPs on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs. The HHS stated that it gave careful consideration to the fact that the members of the DSaRM voted 19 to 10 in favor of rescheduling HCPs from schedule III to schedule II under the CSA. The HHS considered the increasing trends, the public comments, the recommendation of the DSaRM, the health benefits and risks, and the information available about the impact of rescheduling, and concluded that HCPs have high potential for abuse.

[redacted]After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II" which proposed to reschedule HCPs from schedule III to schedule II of the CSA. 79 FR 11037, Feb. 27, 2014. Both the DEA and HHS eight-factor analyses, as well as the DEA's Economic Impact Analysis (EIA), were made available in their entirety in the public docket for this rule (Docket No. DEA-389) and are available at http://www.regulations.gov/#!docketDetail;D=DEA-2014-0005 under "Supporting and Related Material." The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by March 31, 2014. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before April 28, 2014. The DEA specifically solicited comments on the economic impacts of rescheduling with a request that commenters describe the specific nature of any impact on small entities and provide empirical data to illustrate the extent of such impact.

IV. Comments Received

The DEA received 573 comments on the proposed rule to reschedule HCPs. Fifty-two percent (52%) (298 comments) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. Forty- one percent (41%) (235 comments) opposed rescheduling HCPs into schedule II. Seven percent (7%) (40 comments) did not take a definitive position regarding rescheduling of HCPs.

Comments were submitted by a variety of individuals, including among others: Federal and State Government officials, manufacturers, distributors, pharmacies, surgeons, emergency physicians, dentists, physician assistants, nurse practitioners, pharmacists and pharmacy students, ultimate users of HCPs, and members of the general public.6 7 The DEA also received comments from a number of national and regional trade associations with memberships comprised of manufacturers and distributors, pharmacists, pharmacies, physicians, pain specialists, doctors of optometry, physician assistants, nurse practitioners, and long term care facilities (LTCFs). In addition, the DEA received comments from patient advocacy groups. The 5 commenter categories with the most submissions were physicians (13%; 73 comments); mid-level practitioners \8\ (5%; 31 comments); pharmacists and pharmacy students (21%; 122 comments); the general public (44%; 250 comments); and ultimate users (6%; 35 comments).

\6\ The term "ultimate user" means a person who has lawfully obtained, and who possesses, a controlled substance for his own use or for the use of a member of his household or for an animal owned by him or by a member of his household. **21 U.S.C. 802**(27).

\7\ Comments from the "general public" are distinguished from those submitted by "ultimate users" when the commenter did not specifically indicate in their comment that they personally use HCPs.

\8\ The term "mid-level practitioner" means an individual practitioner, other than a physician, dentist, veterinarian, or podiatrist, who is licensed, registered, or otherwise permitted by the United States or the jurisdiction in which he/she practices, to dispense a controlled substance in the course of professional practice. **21 CFR 1300.01**(b).

As discussed above, 52% of all commenters (298 of 573 comments) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. The majority of those supporting the rule were members of the general public and physicians. Comments submitted by the general public comprised 62% of the total 298 comments that supported, or supported with qualification, the rescheduling. Seventy-four percent (74%) (184 of 250 comments) of all comments submitted by the general public were in support, or supported with qualification, the rescheduling. Comments by physicians comprised 14% of the total 298 comments that supported or supported with qualification rescheduling. Fifty-six percent (56%) (41 of 73 comments) of all comments submitted by physicians were in support, or supported with qualification, rescheduling.

[redacted]Forty-one percent (41%) of commenters (235 of 573 comments) opposed the proposal to reschedule HCPs from schedule III to schedule II of the CSA. The majority of those opposed to rescheduling HCPs were pharmacists, pharmacy students, and ultimate users. Pharmacists and pharmacy students comprised 31% of the total 235 comments submitted in opposition to the rule. Sixty percent (60%) (122 comments) of all comments submitted by pharmacists and pharmacy students were in opposition to the rule. Comments from ultimate users comprised 14% of the total 235 comments in opposition to the rule. Ninety-one percent (91%) (32 of 35 comments) of all comments submitted by ultimate users were in opposition to rescheduling.

Further discussions of these comments are included below.

A. Support of the Proposed Rule

Two hundred ninety-eight commenters (52%) supported, or supported with qualification, controlling HCPs in schedule II of the CSA. Forty- one percent (41%) of commenters opposed controlling HCPs in schedule II, and 7% of commenters

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did not have a clearly defined position either in support or in opposition to the rescheduling. The majority of those supporting the rule were members of the general public (62%) and physicians (14%), with 74% of comments from the general public supporting, or supporting with qualification, and 56% of comments from physicians supporting, or supporting with qualification, making HCPs schedule II controlled substances. Manufacturers, pharmacists, mid-level practitioners, pharmacy students, and trade associations also expressed support for the rule. Of all comments submitted, in support and opposition, 40% of pharmacists, 9% of ultimate users, and 78% of the general public were in support.

The State Attorney General and a U.S. Senator from the State with last year's highest per capita rate of prescription drug overdose in the nation wrote in strong support of rescheduling HCPs. The State Attorney General wrote that, "This reclassification is not only justified given the high abuse and addiction potential of hydrocodone prescription painkillers * * *, it is necessary to combat the drug abuse epidemic that is destroying so many [ ] communities. I urge you to proceed with your rulemaking without delay. The abuse of hydrocodone is an urgent problem that necessitates urgent action." The U.S. Senator wrote that, "rescheduling hydrocodone combination drugs would be a tremendous step forward in the fight to curb the prescription drug abuse epidemic that has ravaged * * * our country. It will help prevent these highly addictive drugs from getting into the wrong hands and devastating families and communities * * *. I urge the DEA to move quickly in finalizing its regulations so that we are able to save hundreds of thousands of lives."

Two U.S. Senators from two other States, wrote a joint comment in support of rescheduling, stating that: "As members of the Judiciary Committee and senators from states hit particularly hard by the opioid epidemic, we are well aware of the alarming rates of diversion and prescription drug abuse," and "we fully support DEA's efforts to combat this nationwide public health crisis." All three Senators expressed their desire that patients maintain access to legitimate care.

A major component of the rescheduling of HCPs was to evaluate their abuse potential as required under **21 U.S.C. 812**(b)(2). Many commenters indicated support for controlling HCPs in schedule II based on the scientific evidence demonstrating the high abuse potential of HCPs, evidence that HCPs may lead to severe psychological or physical dependence, history and current pattern of abuse, significance of abuse, and risk to the public health and safety. Of the total 47 commenters who referenced the scientific, medical, and epidemiological data that was used to support the statutory requirement under 21 U.S.C. 812(b)(2) for control of HCPs in schedule II of the CSA, 29 agreed with the data used to support control of HCPs in schedule II. Nineteen commenters specifically discussed the eight-factor analysis that was conducted in support of rescheduling HCPs into schedule II. Ten of those 19 commenters were in agreement with the DEA's analysis. Nine of the commenters who cited the DEA's eight-factor analysis indicated that the presented evidence was congruent with the requirements for placing a drug or other substance into schedule II of the CSA. (One commenter, while in agreement with the conclusion of the eight-factor analysis, did not favor rescheduling HCPs.)

[redacted]Commenters generally agreed that there is psychological and physical dependence associated with HCPs that support placement into schedule II. For example, one commenter stated that rescheduling HCPs from schedule III to schedule II "would be in the best interest of the general public" because he has personally witnessed the increase in abuse of prescription pain medication over the course of his 45-year career as a pharmacist. Additional supportive comments included that the mechanism of action of hydrocodone is identical to oxycodone and morphine, both in schedule II as combination and single-entity products. Some commenters indicated that lower doses of hydrocodone in HCPs do not lower abuse and therefore agreed with the transfer to schedule II. Other commenters mentioned that HCPs are metabolized to hydromorphone, a schedule II opioid, and also have similar mechanisms of action to other schedule II opioids including oxycodone, morphine, and fentanyl, suggesting that abuse potential would be comparable. Some of the commenters indicated that HCPs are more likely to be abused due to their greater availability.

Many of the commenters cited one of their primary reasons for supporting the rule was that it would lead to tighter regulation of HCP prescriptions. For example, one commenter stated: "Hydrocodone combination products should not be available with multiple refills on a single prescription and need to be prescribed more cautiously." Similarly, another commenter stated: "Rescheduling HPCs [sic] would directly address the problem of 'leftover' pills in parents [sic] medicine cabinets, and would keep kids safe. Furthermore, lowering the quantity a doctor can prescribe will decrease the number of drugs that are sold on the street, which will in turn decrease crime and decrease HCP abuse overtime [sic]."

Many of the commenters wrote of their personal experiences with loved ones who suffer or had suffered with abuse and addiction, including many youths and you adults who have tragically died as a result of HCPs or other prescription opioids. The commenters wrote that the path to abuse and addiction was varied--sometim beginning with a practitioner prescribing HCPs, and other times by recreational use of pills that were available for them to access as a result of practitioner overprescribing. Many of these commenters believe that controlling HCPs as a schedule II controlled substance will impose controls necessary to prevent the abus and diversion of HCPs.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

B. Request for Extended Comment Period

The DEA received two comments requesting that the DEA reopen the period for public comment. One of the commenters specifically requested that the comment period be reopened for a minimum of 180 days. The stated justification of one of the commenters was that "[t]he current period is utterly inadequate to large segments of the population who have had no meaningful notice, have extremely limited internet access in small time periods through use of computers at public libraries and are particularly at risk from harm if this rule is adopted." Both requests for extended comment periods were accompanied by meaningful comment along with the request for extension.

DEA response: The Administrative Procedure Act does not set a minimum length of time for public comment. 21 U.S.C. 553; Phillips Petroleum Co. v. U.S. E.P.A., 803 F.2d 545, 558-59 (10th Cir. 1986) (upholding the EPA's refusal to extend the 45-day comment period on an NPRM, noting that courts have uniformly upheld comment periods of 45 days or less) (internal citations omitted). However, both Executive Orders 12866 and 13563 provide that agencies should afford the public a comment period of at least 60 days. The DEA published in the Federal Register the NPRM proposing to reschedule HCPs into schedule II of the CSA on February 27, 2014. 79 FR 11037. The

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DEA provided 60 days for interested persons to submit written comments (either online or through the mail) on the proposal. The comment period closed April 28, 2014. Seven hundred twenty-four submissions on the associated docket at http://www.regulations.gov were submitted by the close of the comment period. Several paper submissions duplicating electronic submissions were received via the mail as well. (The 724 number differs from the finalized number of 573 comments received because, as alluded to above, many commenters submitted multiple, duplicate submissions. Multiple submissions of exactly identical comments submitted by the same person or entity are considered by the DEA as only a single, submitted comment.) Based on the following considerations, the DEA declines to reopen the period for additional public comment.

The Federal Register is published daily, Monday through Friday, except official holidays, by the Office of the Federal Register, National Archives and Records Administration, under the Federal Register Act (44 U.S.C. chapter 15). Section 7 of the Federal Register Act (44 U.S.C. 307) provides that publication in the Federal Register constitutes constructive notice to persons subject thereto or affected thereby. The Federal Register is published in paper and on microfiche. It is also available online at no charge at http://www.gpo.gov/fdsys/.

The NPRM was also available on http://www.regulations.gov to enable the public to conveniently access the proposal and the supporting materials. Of additional consideration, on the same day as publication in the Federal Register, the DEA issued a press release stating that the Administration had published in the Federal Register an NPRM to move HCPs from schedule III to schedule II (available at http://www.justice.gov/dea/divisions/hq/2014/hq022714.shtml). The press release advised individuals where a complete copy of the NPRM could be obtained as well as how they could submit comments in response to the proposal. The DEA accepted written comments submitted either through Regulations.gov or through the mail.

In accordance with the Administrative Procedure Act, the DEA's published NPRM included "the terms or substance of the proposed rule" and "a description of the subject and issues involved." 5 U.S.C. 553(b)(3). The quality and quantity of the responses received in response to the published NPRM, as well as the variety of respondents, including those advocating on behalf of persons residing in LTCFs and other populations that may potentially feel distributional regulatory impacts, demonstrate to the DEA that there has been an adequate opportunity for meaningful public participation by interested persons in accordance with the Administrati Procedure Act. 5 U.S.C. 553(c); Idaho Farm Bureau Fed'n v. Babbitt, 58 F.3d 1392, 1404 (9th Cir. 1995) (holding that comments discussing the proposed action a supporting data were evidence that the public had obtained and reviewed the information and thus adequate opportunity for public comment had been given).

The DEA notes that the submission by a nurse located in Australia shows that the published NPRM was widely read and reviewed. In addition, those commenters requesting additional time for comment accompanied their request for an extension with substantial comment on the rule. This demonstrates to the DEA that adequate notice and opportunity for meaningful comment was provided by the DEA on this rulemaking.

C. Clarification of Affected Drugs and Substances

The DEA received some comments, though limited in number, indicating it would be helpful to provide detailed discussion of what products are affected by this rule. One commenter specifically requested clarification as to whether the action would apply to cough syrups that contain hydrocodone. The second commenter requested the DEA not change the schedule of ZohydroTM ER. The third commenter requested that Zogenix, the manufacturer of ZohydroTM ER, be "allow[ed] to bring their new drug to market."

DEA response: This rulemaking action affects hydrocodone combination products, which are those substances described in **21 CFR 1308.13**(e)(1) (iii) and (iv). All other products containing hydrocodone are already controlled in schedule II of the CSA and are not impacted by this action. ZohydroTM ER does not meet the definition of either 21 CFR 1308.13(e)(1) (iii) or (iv); it is currently a schedule II controlled substance under **21 CFR 1308.12**(b)(1)(vi) and is not affected by this action.

Other than ZohydroTM ER, all pharmaceuticals containing hydrocodone currently on the market in the United States are HCPs and are subject to this rulemaking. Hydrocodone is the most frequently prescribed opioid in the United States with nearly 137 million prescriptions for HCPs dispensed in 2013. IMS Health, National Sales PerspectiveTM (NSP). There are several hundred brand name and generic hydrocodone products marketed with the most frequently prescribed combination being hydrocodone and acetaminophen (e.g., Vicodin[supreg], Lortab[supreg]). Currently marketed HCPs approved as cough suppressants include Hycodan[supreg], Mycodone[supreg], Tussionex[supreg], Pennkinetic[supreg], Tussigon[supreg], and several generics.

D. Opposition to the Proposed Rule

Two hundred thirty-five commenters (41% of all commenters) opposed the proposal to reschedule HCPs from schedule III to schedule II of the CSA. Many comments submitted in opposition came from pharmacists, including pharmacy school students/interns (31%); the general public (23%); and ultimate users (14%). Of all comments submitted, in support and in opposition, 60% of pharmacists were opposed; 22% of the general public were opposed; and 91% of ultimate users were opposed. These commenters opposed the rescheduling HCPs for a variety of reasons. The comments in opposition can be grouped in the following general categories: (1) Concerns over the DEA's authority to reschedule HCPs; (2) concerns over prescribing practices; (3) concerns regarding patient access to medicine; (4) concerns regarding impacts at LTCFs; (5) concerns that rescheduling HCPs will not prevent abuse or diversion; (6) concerns that rescheduling HCPs will increase provider and pharmacist workload; (7) concerns regarding economic impacts to manufacturers, distributors, pharmacies, physicians, and ultimate users; (8) concerns that alternatives to rescheduling had not been explored and/or implemented first; and (9) concerns about the amount of time to comply with the rule. Each of these general categories is addressed below.

1. Authority To Control Drugs or Substances

a. DEA's Authority To Schedule Substances

One commenter questioned the DEA's general authority to schedule drugs.

DEA response: Recognizing the need for a high level of scrutiny over controlled substances due to their potential for abuse and danger to the public health and saf Congress established a closed system of distribution for all controlled substances with the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970. See H.R. Rep. No. 91-1444, 1970 U.S.C.C.A.N. at 4566. The DEA

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implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. 28 CFR 0.100. 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 [**21 U.S.C. 812**(b)] 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 the DEA. The DEA's authority to implement and enforce the CSA, including adding to the schedules, has been repeatedly recognized and upheld in the Courts. E.g., U.S. v. Alexander, C.A.9 (Cal.) 1982, 673 F.2d 287 (1982), cert. denied, 459 U.S. 876 (Congress' delegation to Attorney General of authority to reclassify controlled substances is constitutional); U.S. v. Roya, C.A.7 (Ill.) 1978, 574 F.2d 386, cert. denied, 439 U.S. 857 (finding no merit to the claim that the addition and reclassification of amobarbital and phenmetrazine as schedule II controlled substances by the Attorney General was an unconstitutional delegation of authority under separation of powers doctrine); U.S. v. Kinder, C.A.5 (Tex.) 1991, 946 F.2d 362, cert. denied, 503 U.S. 987, cert. denied, 504 U.S. 946, rehearing denied, 505 U.S. 1238 (Attorney General followed proper procedures in reclassifying methamphetamine as schedule II controlled substance, pursuant to the CSA; Attorney General properly delegated his authority to the Director of the Bureau of Narcotics and Dangerous Drugs (BNDD) who then reclassified methamphetamine).

b. Conflict With Other Federal Law

One commenter questioned whether the rescheduling action would have illegal discriminatory effects, and "violate laws against disability and age discrimination." This same commenter also asserted without premise that the rescheduling action could potentially conflict with parts of the Affordable Care Act and "deprivation of rights under color of authority."

DEA response: Executive Order 12866 of September 30, 1993, "Regulatory Planning and Review," and Executive Order 13563 of January 18, 2011, "Improving Regulation and Regulatory Review," direct Federal agencies to assess costs and benefits of available regulatory alternatives and, if the regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). Paragraph (b)(1) of section 1 of Executive Order 12866 specifically directs Federal agencies to "avoid regulations that are inconsistent, incompatible, or duplicative with its other regulations or those of other Federal agencies." The DEA has reviewed the impacts of this scheduling action against the principles edified by Executive Orders 12866 and 13563 and finds no basis that it would have illegal discriminatory effects, or "violate laws against disability and age discrimination."

c. Factors Determinative of Control

Twenty-six commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns regarding the eight-factor analyses. Twenty-four commenters believed that the eight-factor analyses did not support rescheduling into schedule II and that HCPs should remain in schedule III. Two commenters believed that HCPs should be rescheduled into a lower schedule than schedule III. (One commenter stated that HCPs should be down-scheduled into schedule V and made over-the-counter for those 21 years and older.)

i. Evaluation of Abuse Potential of HCPs and Data Used To Support Placement of HCPs into Schedule II of the CSA

Eighteen commenters expressed disagreement about the data that was used to support the statutory requirement under **21 U.S.C. 811**(c) and **812**(b)(2) for placement into schedule II of the CSA. Some of these commenters stated that the available data are limited and do not support rescheduling HCPs into schedule II. Some commenters indicated that there was no scientific consensus in support of moving HCPs from schedule III to schedule II.

Many of the comments in opposition to the proposed scheduling action were statements by ultimate users of HCPs that HCPs are not abused by patients with legitimate prescriptions. Some of the commenters stated that the small amounts of hydrocodone in HCPs have never contributed to addiction and acetaminophen in HCPs would actually decrease abuse rates. Commenters suggested that abuse potential of HCPs is lowered or negated by the fact that it is often used with other substances such as alcohol. Some commenters supported their assertions with statements that deaths are extremely rare with HCPs.

DEA response: The DEA conducted a comprehensive evaluation of epidemiological, diversion, pharmacological, and pharmacokinetic data to conclude that HCPs have a high abuse potential. All of the data was reviewed collectively, and the data supports the finding that HCPs have a high abuse potential similar to other schedule II controlled substances, such as oxycodone products. The DEA's decision to reschedule HCPs from schedule III to schedule II is also supported by the HHS review and the FDA's DSaRM recommendation.

The DEA disagrees that there is a lack of scientific consensus among scientific experts. Some commenters, in support of their dissenting opinions, cited some selective information presented in the briefing document for the FDA's DSaRM meeting in January 2013. It should be noted that the DSaRM members received the selected information cited by the commenters, and, upon deliberating extensively on all the available data voted 19 to 10 in favor of rescheduling HCPs from schedule III to schedule II. The DEA's determination of the appropriate schedule under the CSA in which to place HCPs is based on a comprehensive review of all available data, rather than selected portions of available data, and the DEA did in fact review and consider the selected information presented by the commenters. The DEA also considered the HHS scientific and medical evaluation and scheduling recommendations.

The DEA finds that the scientific, medical, and epidemiological data are robust and support rescheduling HCPs into schedule II of the CSA. Various drug abuse indicators for HCPs indicate that HCPs are widely diverted and abused at rates largely similar to that of oxycodone products (schedule II). The data indicate that HCPs have an abuse potential similar to schedule II opioid analgesics such as oxycodone and their abuse is associated with severe psychological or physical dependence. Abuse of HCPs is also associated with large numbers of individuals being admitted to addiction treatment centers. Individuals are taking these drugs in sufficient quantities to create a hazard to their health, and abuse of HCPs is associated with large numbers of deaths. Further, data from several different drug abuse monitoring databases support the conclusion that HCPs have a high potential for abuse similar to other schedule II opioid analgesics.

Contrary to the views expressed by some commenters, the review by the DEA and HHS of all the relevant data found that HCPs are abused at high rates and have high dependence potential as indicated by the data reported by the National Survey on Drug Use and

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Health (NSDUH), Monitoring the Future (MTF), National Poison Data System (NPDS), Drug Abuse Warning Network (DAWN), and Treatment Episode Data Set (TEDS). There have been large numbers of deaths and emergency department visits associated with abuse of HCPs. In addition, the data indicate that HCPs and oxycodone products have similar abuse potential. Based on these considerations, the DEA believes that the high abuse and dependence potential and harm associated with HCPs support rescheduling into schedule II of the CSA.

Contrary to statements made by some ultimate users, even low doses of HCPs have the potential for adverse impacts on the public health and safety. According to the CDC, while an estimated 80% of patients who are prescribed opioids are prescribed low doses (<100 mg morphine equivalent dose per day) by a single practitioner, these patients account for an estimated 20% of all prescription drug overdoses.\9\ (An estimated 10% of patients who are prescribed opioids are prescribed high doses (>=100 mg morphine equivalent dose per day) by single prescribers. These patients account for an estimated 40% of all prescription opioid overdoses. An estimated 10% of patients are patients who seek care from multiple doctors and are prescribed high daily doses of opioids. They account for another 40% of all opioid overdoses.) Id.

\9\ Centers for Disease Control, CDC Grand Rounds: Prescription Drug Overdoses--a U.S. Epidemic, 61(01) Morbidity and Mortality Weekly Report (MMWR) 10 (2012) (internal citations omitted) available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm.

After careful consideration of relevant data, the DEA finds that HCPs have abuse potential supporting placement into schedule II.

ii. Criteria for Abuse

One commenter wanted the DEA to draw distinctions among abuse, addiction, and dependence. A second commenter objected to the DEA's consideration of "individuals taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs" as a criterion of abuse.

DEA response: As noted by researchers, "[t]here is no agreement between researchers for terms such as drug abuse, psychological dependence, drug dependence and drug addiction," and that, "[o]ften these terms are used interchangeably." \10\ The DEA is aware that the most recent version of the Diagnostic and Statistical Manual, the DSM- V, released in 2013, removed the distinction between abuse and dependence for diagnostic purposes, and replaced them with a combined single disorder called "substance use disorder." However, the DEA derives authority from the CSA, and when acting under its authority must speak under the terms and conditions imposed by it. The CSA does not define "abuse" in terms of the DSM; in fact it does not define the term at all. The CSA uses terms such as "potential for abuse," "pattern of abuse," and "significance of abuse." E.g., **21 U.S.C. 811** and **812**.

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\10\ Laxmaiah Manchikanti, MD et al., National All Schedules Prescription Electronic Reporting Act (NASPER): Balancing Substance Abuse and Medical Necessity, 5 Pain Physician 294, 299, n.3 (2002).

One looks first to the face of a law to understand its meaning, and "[i]f the statute's meaning is plain and unambiguous, there is no need for further inquiry." United States v. Fisher, 289 F.3d 1329, 1337-38 (11th Cir.2002) (internal quotation marks and citation omitted). However, if the language is ambiguous, the relevant legislative history may be used to aid in understanding meaning. United States v. Dodge, 597 F.3d 1347, 1352 (11th Cir. 2010). The legislative history of the CSA suggests four factors that may be considered in determining whether a particular drug or substance has a "potential for abuse," including whether individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.\11\ Accordingly, the DEA uses this as one factor in determining a substance's potential for abuse.

\11\ As provided in the CSA's legislative history:

* * * [A] substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect if: (1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or (2) There is a significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or (3) 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 (4) 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.

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

"Addict" is defined by the CSA as a person who "habitually uses any narcotic so as to endanger the public morals, health, safety, or welfare, or who is so far addicted to the use of narcotic drugs as to have lost the power of self-control with reference to his addiction." **21 U.S.C. 802**(1). The DEA uses this definition for the terms "addict" and "addiction."

iii. Appropriate Drug Comparator

One commenter asserted that HCPs were not compared to appropriate reference drugs and have lower abuse ratios and abuse potential than schedule II oxycodone combination products. Another commenter expressed the opinion that HCPs are substantially cheaper than oxycodone products which would affect drug selection as opposed to the notion that HCPs have more addiction potential. The commenters did not provide any appropriate alternative comparison drug for HCPs.

DEA response: HCPs were compared to oxycodone products, currently schedule II controlled substances, to evaluate abuse potential. The DEA, in agreement with the HHS review, considers the comparison of HCPs to oxycodone products appropriate due to similarities between their pharmacological properties, therapeutic uses and patterns, as well as market history. In their eight-factor analysis, the FDA noted that it is not always possible to identify an "appropriate opioid comparator in Schedule III." The FDA went on to state that: "While FDA considered codeine as a potential comparator, it was deemed inappropriate for several reasons * * *. Given the absence of an appropriate Schedule III comparator, FDA focused its analyses on comparing the abuse liability of hydrocodone combination products (Schedule III) with oxycodone products (Schedule II)."

With regard to the comment about the lower costs of HCPs contributing to its high abuse potential, it is important to note that abuse potential of a given drug is also influenced by various other factors (e.g., pharmacological properties, ease of availability, etc.). Additionally, actual abuse data comparing HCPs and oxycodone combination drugs indicate that the abuse potential between the two drugs is similar. Contrary to the views expressed by some commenters, the review by the DEA of all the relevant data found that HCPs are abused at high rates and have high dependence potential as indicated by the data

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reported by the NSDUH, MTF, NPDS, DAWN, and TEDS. There have been large numbers of deaths and emergency department visits associated with abuse of HCPs. Based on these considerations, the DEA believes that the high abuse and dependence potential and harm associated with HCPs support rescheduling into schedule of the CSA.

iv. Balanced Presentation of the Eight-Factor Analysis

Nine commenters disagreed with the conclusions in the DEA's eight- factor analysis. These commenters asserted that the DEA's eight-factor analysis was not a balanced presentation and did not include the therapeutic benefits or the negative impact on patients with a legitimate medical use for HCPs. In addition, some of the commenters stated that the DEA's eight-factor analysis used flawed analytical methods and failed to show that HCPs were more dangerous or more abused than oxycodone. Several of these commenters requested that DEA include both sides of the clinical argument and peer-reviewed clinical research.

DEA response: The DEA reviewed the required eight factors in accordance with the provisions stated in **21 U.S.C. 811**(c), specifically exploring the abuse potential and potential harms of HCPs. The DEA's analysis also acknowledges that there is a currently accepted medical use, and accordingly therapeutic benefit, of HCPs. Consistent with the CSA, an evaluation of abuse and dependence potential, risk to the public health and safety, and other factors are included in the analysis. 21 U.S.C. 811(c). The CSA does not require that HCPs be more dangerous or abused than oxycodone in order to be placed in schedule II. Rather, relative abuse potential must be established. The DEA's analysis shows that HCPs have a high potential for abuse, and the abuse potential of HCPs is comparable to the schedule II controlled substance oxycodone. Thus, HCPs are appropriately placed in schedule II, along with oxycodone. Further, the analytical methods that were presented in the DEA's eight-factor analysis were consistent with the HHS's eight- factor analysis that was finalized in December 2013. The DEA used the best available methods based on current science to complete the eight- factor analysis.

2. Requirements Applicable to Prescriptions

a. Authority To Prescribe HCPs as Schedule II Controlled Substances

Nineteen commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns related to the restricted authority of mid-level practitioners to prescribe medications that are schedule II controlled substances.

DEA response: The DEA recognizes that some States do not allow all providers to prescribe schedule II controlled substances. However, it is outside of the DEA's scope of authority under the CSA to determine what categories of practitioners may prescribe controlled substances. Under the CSA, it is up to each State to decide who has the authority to prescribe controlled substances within that State. This is reflected in **21 U.S.C. 823**(f), which requires DEA to register a practitioner who is authorized under the laws of the State in which he practices unless the practitioner's registration would be inconsistent with the public interest. 21 U.S.C. 823, **824**. This is also echoed in **21 CFR 1306.03**, which states that a practitioner can issue a prescription for controlled substances so long as the practitioner is authorized to prescribe controlled substances by the jurisdiction where he is licensed to practice his profession and is registered or exempted from registration pursuant to **21 CFR 1301.22** (c) and **21 CFR 1301.23**. Each State has this authority, so long as it does not conflict with federal law.

b. Transmittal Method of HCPs as Schedule II Controlled Substances

i. Oral and Facsimile Prescriptions

Multiple commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns related to the transmittal methods available for schedule II as compared to schedule III controlled substances, specifically the circumstances required in order to provide oral prescriptions and to transmit prescriptions via facsimile. Both ultimate users and providers expressed concern that HCPs as schedule II controlled substances will not be available on nights and weekends. They were especially concerned about dental emergencies that might occur over the weekend. Four commenters stated that patients needing night or weekend prescriptions for HCPs will overburden Emergency Departments (EDs).

DEA response: The requirements for issuing an emergency oral prescription for a schedule II controlled substance do not hinder legitimate access to HCPs. The procedural requirements relating to transmission of a legitimate prescription do not hinder legitimate access either.

Contrary to concerns of commenters, practitioners will still be allowed to call-in prescriptions for HCPs in the event of an emergency. In the event of an emergency, as defined by 21 CFR 290.10, a pharmacist may dispense a schedule II controlled substance upon receiving oral authorization of a prescribing individual practitioner in accordance with **21 CFR 1306.11**(d).

ii. Triplicate Prescriptions

Five commenters opposed rescheduling HCPs as schedule II controlled substances based on concerns regarding "triplicate prescriptions." One commenter stated that emergency physicians do not have triplicate prescription forms, and as a result, they will be required to prescribe drugs that are less effective for pain management. Two commenters stated that emergency physicians do not want to carry a triplicate prescription pad.

DEA response: Neither the CSA nor DEA regulations require prescriptions to be prepared in triplicate. The DEA recognizes that some States, such as Texas and California, require the use of triplicate prescription forms for some or all controlled substances. As stated in the November 19, 2007, final rule, "Issuance of Multiple Prescriptions for Schedule II Controlled Substances," the "DEA supports the efforts of States to take the specific action they deem necessary to prevent the diversion of controlled substances within their jurisdictions." 72 FR 64921, 64923.

> Under the CSA, Congress envisioned that the Federal and State Governments would work in tandem to regulate activities relating to controlled substances. This is reflected in **21 U.S.C. 903**, which indicates that Congress did not intend to preempt state controlled substance laws, so long as such state laws do not conflict with federal law. Thus, each state may enact controlled substance laws that go beyond the requirements of the CSA, provided such laws do not conflict with the CSA. Given this aspect of the CSA, it would not be appropriate for DEA to seek to preempt or supersede state laws relating to the prescribing of controlled substances, provided such laws do not conflict with the CSA or DEA regulations.

Id. at 64927.

c. Quantity and Frequency of Fills and Refills for HCPs as Schedule II Controlled Substances

Pharmacists, prescribers, and ultimate users expressed concern about the quantity and frequency of fills and refills for HCPs as schedule II controlled substances that would be allowed if HCPs were placed into schedule II.

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Several commenters, mostly ultimate users, asserted that up-scheduling would result in patients being limited to a 30-day supply of medication and would correspondingly need to begin seeing their doctors monthly. Other commenters, primarily pharmacists and physicians, expressed their belief that rescheduling HCPs will result in larger quantities of pills being authorized on each prescription to prevent patients from running out of medication and being in pain. Most of these commenters had corresponding concerns that these larger prescriptions would lead to more unused medication in the home that would be available for diversion. Examples include the following: One commenter mentioned his concern that since larger prescriptions would be authorized, he would be unable to monitor whether the patient is taking the medication or taking too much of it. An emergency physician opined that removing the ability to get refills on HCPs may result in prescriptions for more potent medications being issued. One ultimate user was concerned that the elimination of refills on HCPs would result in patients getting insufficient quantities to treat the acute illness for which it was prescribed.

DEA response: While courts have recognized that prescribing an "inordinately large quantity of controlled substances" can be evidence of a violation of the CSA,\12\ generally neither the CSA nor DEA regulations impose a specific quantitative minimum or maximum limit on the amount of medication that may be prescribed on a single prescription, or the duration of treatment intended with the prescribed controlled substance. The quantity prescribed and dispensed is limited in an emergency situation as defined by 21 CFR 290.10 when dispensing a schedule II controlled substance upon oral authorization in accordance with **21 CFR 1306.11**(d). The CSA and implementing regulations require all controlled substance prescriptions to be "valid." A prescription is not "valid" unless it is issued for a legitimate medical purpose and within the usual course of professional practice. **21 CFR 1306.04**(a). A pharmacist who fills a prescription has a corresponding responsibility, and the person who fills an illegitimate prescription is subject to penalty. Id.

\12\ United States v. Rosen, 582 F.2d 1032, 1036 (5th Cir. 1978).

While the CSA and DEA regulations generally contain no specific limit on the quantity that may be prescribed on a single prescription, or the duration of treatment intended for a single prescription, some States do impose specific limits on prescribing schedule II controlled substances. Likewise, some limitations on the quantity or frequency of schedule II controlled substances may be limited by individual prescription benefit providers. Any limitations imposed by State law apply, in addition to the corresponding requirements under Federal law, so long as the State requirements do not conflict with or contravene the Federal requirements. **21 U.S.C. 903**; **21 CFR 1306.12**(b)(1)(v); "Clarification of Existing Requirements Under the Controlled Substances Act for Prescribing Schedule II Controlled Substances," 70 FR 50408, Aug. 26, 2005.

Although the CSA prohibits refills of prescriptions for schedule II controlled substances, a practitioner may issue multiple schedule II prescriptions in order to provide up to a 90-day supply of medication in accordance with **21 CFR 1306.12**. Furthermore, DEA regulations do not require patients to be seen monthly by their provider. Rather, practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards how often to see their patients when prescribing controlled substances.

Note, however, that DEA regulations should not be "construed as mandating or encouraging individual practitioners to issue multiple prescriptions or to see their patients only once every 90 days when prescribing Schedule II controlled substances. Rather, individual practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards, whether it is appropriate to issue multiple prescriptions and how often to see their patients when doing so." **21 CFR 1306.12**(b)(2). The DEA does not regulate the general practice of medicine and the agency lacks the authority to issue guidelines (or make policy statements) that constitute advice on the general practice of medicine.

3. Patient Access to Medicine

The DEA received numerous comments, predominantly from ultimate users, who voiced concerns about the possible effects rescheduling would have on patients' access to appropriate treatment for pain. Commenters were concerned about the possible need for increased provider visits, and associated increased time and cost to receive medical care. Commenters were concerned about access to health care providers, such as possibly needing to change health care providers and in some cases having to drive longer distances to get to practitioners' offices because of limitations on types of practitioners who can prescribe schedule II controlled substances. Commenters were also concerned that rescheduling could result in doctors changing prescriptions to alternative medications which might be less effective for treating some kinds of pain and/or cause adverse health effects.

a. Impact on Prescribing Practices

Several commenters were concerned that because of the rescheduling, practitioners will be less likely to prescribe HCPs. One commenter suggested that since a practitioner can no longer call in or fax a prescription to the pharmacy, the practitioner will be reluctant to prescribe HCPs. Other commenters stated the scheduling action will impose additional burdens on practitioners and therefore they will stop prescribing for HCPs and prescribe less effective drugs. One commenter stated that many EDs do not typically prescribe schedule II narcotics. Likewise, two commenters suggested that cumbersome and slow ordering processes for schedule II substances will cause local shortages of HCPs, and thus practitioners will turn to prescribing other drugs.

DEA Response: The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination of whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, controlling HCPs as a schedule II controlled substance should not hinder legitimate access to the medicine. As recognized and noted by commenters, scheduling a medication does not make it impossible to prescribe, dispense, or administer the medication. However, it does alert prescribing- practitioners, pharmacists medical support professionals and perhaps even some patients and non-professional caregivers that the medication has potential dangers for addiction and misuse, and careful monitoring and evaluation of use of such drugs is necessary for appropriate patient care. "The placing of a drug into [a particular schedule of the CSA] will alert a physician that the drug does cause physical and psychological dependence. This is valuable information for a physician to possess before prescribing any drug." 50 FR 8104, 8107, Feb. 28, 1985 ("Schedules of Controlled Substances; Rescheduling of Buprenorphine From Schedule II to Schedule V of the Controlled Substances Act").

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The DEA does not intend for legitimate patients to go without adequate care. A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a). When a practitioner prescribes a medication that is a controlled substance for a patient, it must be because he/she has made a professional medical determination that it would be medically appropriate for the patient's medical condition to treat with that specific controlled substance.

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The DEA recognizes that rescheduling a legitimately marketed pharmaceutical controlled substance may have some effect on the decision of a practitioner to prescribe that particular controlled substance. There may be some practitioners who are reluctant to prescribe a schedule II controlled substance although authorized by State law to do so. However, the DEA notes that other schedule II controlled substances are widely prescribed. Given that classification has not deterred practitioners from prescribing those drugs, the DEA believes that when a practitioner makes a medical determination that a particular controlled substance is appropriate to treat a patient's medical condition, the practitioner will prescribe the appropriate controlled substance, regardless of the substance's schedule. The DEA notes that a doctor from New York, one of the States that has already scheduled HCPs as schedule II controlled substances under State law, asserted in his comment that up-scheduli "has reduced unconscious (or conscience-less) prescribing without impacting patients' access to medications."

b. Impact of Criminal Action

Some commenters expressed concern that transferring HCPs to schedule II would deter prescribers from properly treating pain for fear of facing criminal action. According to one commenter, many providers limit the number of pills for schedule II medications "because they feel they are being watched by monitoring progra and are afraid the DEA 'will investigate' them for too many CII scripts."

DEA response: One of the most important principles underlying the CSA is that every prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a); U.S. v. Moore, 423 U.S. 122 (1975) (holding registered physicians may be prosecuted for violation of the CSA when their activities fall outside the usual course of professional practice). The DEA policy statement entitled "Dispensing Controlled Substances for the Treatment of Pain," 71 FR 52715, Sept. 6, 2006, makes clear that this longstanding requirement should in no way interfere with the legitimate practice of medicine or cause any practitioner to be reluctant to provide legitimate pain treatment. Practitioners (as well as ultimate users) become subject to administrative, civil, and/or criminal action when their activity involving controlled substances is not authorized by, or is in violation of, the CSA, regardless of whether the activity involves a schedule II controlled substance or a schedule III controlled substance.

c. Impact on Drug Availability

Two commenters suggested this rule will result in limited drug availability because wholesalers are limiting distributions to community pharmacies. These commenters assert that if a pharmacy goes over a pre-determined amount, they cannot obtain the needed pharmaceuticals until the following month. The commenter asserted that this practice may have particularly adverse impacts in rural areas where a pharmacy may only be serviced by one distributor. Another commenter suggested there will be local shortages of HCPs because of the cumbersome and slow schedule II ordering process. Two commenters were concerned that limited availability may result from delays associated with manufacturer production due to annual production requirements for schedule II controlled substances.

DEA response: DEA registered distributors are required to provide effective controls against diversion of controlled substances. However, the DEA does not limit the quantity of controlled substances that may be legitimately distributed to pharmacies. Any arbitrary limits placed on community pharmacies by distributors are the result of a business decision of that distributor.

The DEA does impose requirements for distributors to operate a system to disclose suspicious orders of controlled substances. **21 CFR 1301.74**(b). Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency. Id. Part of the due diligence associated with that requirement, as well as the general requirement under **21 CFR 1301.71**(a) for registrants to "provide effective controls and procedures to guard against theft and diversion of controlled substances," is to "know your customer." While order volume may be one indicator of a suspicious order, the totality of circumstances must be used in making a determination. Generally, no single indicator is independently a suggestion that a given order is suspicious. Order volume should be examined not only on an industry-wide comparison level, but also on a local level. For example, a pharmacy located near an oncology clinic may be more likely to regularly order higher volumes of certain controlled pharmaceuticals than one that is not.

The DEA does not find evidence to support the claim that the ordering process for schedule II controlled substances will result in limited availability of HCPs. A DEA Form 222, or its electronic equivalent--the Controlled Substance Ordering System (CSOS), is required for all distributions of schedule I or II controlled substances, with specific exceptions, **21 U.S.C. 828**(a); **21 CFR 1305.03**, which enables the DEA to monitor the flow of these controlled substances from their point of manufacture through commercial distribution. It takes approximately an hour to complete each order using the paper DEA Form 222. It takes approximately three minutes to complete an order using CSOS. (The DEA Form 222 permits ten line items per form; electronic orders are not subject to the same requirement and may contain an unlimited number of transactions (line items)). While CSOS transactions are faster, the paper DEA Form 222 orders are also able to be processed quickly through the system. In 2013, 109,632 registrants ordered schedule I or II controlled substances. About 4.8 million orders were processed on Form 222s and 924,2 were processed electronically via CSOS (approximately 16% of all orders). The paper orders represented roughly 27.7 million transactions (or about 6 per order); electronic orders represented roughly 21.2 million transactions or slightly more than 23 per order.

There should be no impact on availability due to schedule II annual production requirements (i.e., manufacturing quota). Registrants that manufacture hydrocodo are already required to obtain an annual quota in order to manufacture hydrocodone because it is a schedule II controlled substance unless and until it is formulate into dosage form HCPs.

Manufacturing quotas are issued to bulk manufacturers who manufacture either from synthetic routes (e.g., hydrocodone from codeine), or extraction from narcotic raw material.

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Bulk manufacturing quota will not be impacted by the movement of HCPs from schedule III into schedule II.

Procurement quotas are typically issued to dosage form manufacturers and repackagers or relablers for manufacturing activities. As related to HCPs, a procurement quota is required to: (1) Receive bulk Active Pharmaceutical Ingredients to be manufactured into dosage units; and (2) for a company to receive bulk finished dosage units for relabeling or repackaging.

d. Providers Authorized To Prescribe Schedule II Controlled Substances

Nine commenters expressed concern about the ability to access health care providers who can prescribe schedule II controlled substances. Specifically, commenters stated that mid-level health care providers such as physician assistants and nurse practitioners, who provide primary health care, cannot prescribe schedule II controlled substances in many States. As a result, these patients will not have access to the medicine they need to treat their pain. In addition, one commenter stated this will have a negative impact on patients who visit rural practices where mid-level practitioners often prescribe pain medication. Moreover, one commenter stated the scheduling action would make it mandatory for a patient to see a physician for pain. Another commenter stated that because of this scheduling they would now have to find new doctors, which would increase travel time and the amount of money spent on gas.

DEA response: State authorization to handle controlled substances is both a necessary precondition for Federal authorization to handle controlled substances and a qualifying determinate as to the extent of the practitioner's scope of authority in regard to such substances. U.S. v. Moore, 423 U.S. 122, 141 (1975) ("The federal registration, which follows automatically, extends no further [than the scope of authority granted by the State to practice medicine and to dispense drugs in connection with their professional practice]."). A DEA registered practitioner may only engage in those activities involving controlled substances that are authorized by the laws of the State on which the practitioner's Federal registration is based. If an individual practitioner, or a class of practitioners, has not been granted authorization to prescribe certain controlled substances that is the rightful determination of the State under its authority to regulate the practice of medicine.

e. Treatment for Pain

Concerns were raised that changes in the scheduling for HCPs could drive the use of alternative treatments. One class of commenters who were particularly concerned about this was emergency physicians who work in States that require triplicate prescriptions and/or facilities whose policy is not to handle schedule II controlled substances in their emergency departments. Some emergency providers in triplicate- prescription States said that they did not carry triplicate prescriptions due to concerns about them being stolen. Some emergency physicians who work in States that require triplicate prescription forms (but who are able to write schedule II controlled substance prescriptions while working in their emergency departments) stated that if "forced to get a triplicate," then he will start writing for more schedule II controlled substances, such as Percocet, because it is a "better pain med[icine] than HCPs." Other commenters were concerned that some prescribers might switch to prescribing "stronger drugs with significant abuse potential," or alternatively switch to medications such as non-steroidal anti-inflammatory drugs (NSAIDs) which are less effective for treating some kinds of pain and may cause other adverse effects, leaving people in untreated pain. One commenter was concerned that trama would be prescribed in place of HCPs, which worried them because of issues with tramadol specific to renal patients.

DEA response: The DEA does not regulate the general practice of medicine and the agency lacks authority to issue guidelines (or make policy statements) that constitute advice on the general practice of medicine. A prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. **21 CFR 1306.04**(a); U.S. v. Moore, 423 U.S. 122 (1975). A practitioner must use sound medical judgment to determine which controlled substance they will prescribe to appropriately treat his or her patient's medical condition, rather than make a determination based upon whether a triplicate prescription form is required by the State or by their employer's policy to not prescribe schedule II controlled substances.

f. Shift to the Black Market

Several commenters stated that making HCPs schedule II controlled substances would limit access to HCPs, causing people to buy drugs on the street, including HCPs and heroin.

DEA response: As discussed above, schedule II controlled substances are readily available for legitimate medical use.

g. Monitoring Access

A national advocacy group for cancer patients requested that the DEA "require monitoring plans and an annual report to Congress, in the event that HCPs are upscheduled, that assess the impact on access by patients with legitimate needs, as emphasized and urged by HHS" and to "adjust policy accordingly if it finds that access is impeded for patients who legitimately need HCPs for pain management."

DEA response: Once upscheduled the DEA will continue to monitor the diversion of HCPs. However, it is outside the scope of the DEA's authority under the CSA to require monitoring plans or reports not authorized under the Act.

4. Impacts on Unique Populations

The DEA received several comments regarding the impact on patients who suffer from chronic pain, cancer, rare diseases, chronic and end- stage renal disease, as well as dental and surgical post-op patients, and rural residents. Many commenters also voiced concerns about possible effects of rescheduling on the elderly and disabled. Several commenters who are affected by chronic pain voiced a concern that the scheduling action will be a burden and make it harder for them to obtain their medicine. As a result, these commenters stated they will suffer solely because of the people that abuse HCPs. Another commenter stated that because of this burden, patients might start self- medicating. One commenter said that practitioners will start prescribing drugs that are not as effective as HCPs, which could have a negative impact on patients mentally. One commenter stated that many cancer patients are in chronic pain, and because of this action, these patients will suffer as they cannot get their required medication. Others suggested post-op patients will have to suffer in pain after their surgeries because they will not be able to get the required medications from doctors on weekends. Several commenters stated that patients in rural areas who are currently seen by mid-level practitioners will need to drive an hour or more to be treated by a physician because their mid-level provider is not authorized to issue prescriptions for schedule II controlled substances. In addition, another commenter stated that many rural physicians are already

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overbooked, which will cause rural patients to suffer in pain until they can get an appointment. Another commenter stated that rural patients have a tough time physically picking up handwritten prescriptions. Several commenters noted that the nearest doctor is more than an hour away and that having to drive that distance once a month to obtain HCPs is inconvenient.

DEA response: Scheduling determinations are based on scientific determinations regarding the substance's potential for abuse, its potential for psychological and physical dependence, and whether the substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based merely on the population it is intended or approved to treat.

5. Impact on Long-Term Care Facilities (LTCFs)

a. Treatment for Pain

Many commenters, including two U.S. Senators, requested that the DEA closely examine possible impacts of rescheduling HCPs in the long- term care facility (LTCF) setting. Many commenters had concerns that placing HCPs into schedule II will impact a substantial number of LTCF residents and may result in untreated pain due to the lack of ready- access to other appropriate medications. For example, according to one commenter, "HCPs are the current, albeit less preferred alternative because of its combination with acetaminophen, which has to be restricted in older adults due to toxicity risk. However, long-term care providers have been forced to use HCPs as a substitute for Schedule II drugs" because they are more readily available for administration due to less restrictive handling requirements for controlled substances in lower schedules than schedule II. According to this same commenter, "the remaining pain care options still in schedule II are not as clinically effective in treating pain for the elderly as HCPs."

Two commenters stated that LTCF residents, especially post-surgical patients, need medications immediately and that obtaining prescriptions is not quick because most LTCFs do not operate with in-house doctors on site.

DEA response: As previously discussed, scheduling determinations are based on scientific determinations regarding the substance's potential for abuse, its potential for psychological and physical dependence, and whether the substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). Nonetheless, the DEA has promulgated many regulations to accommodate the unique circumstances of LTCF residents. For example, in accordance with **21 CFR 1306.11**(f), a prescription for a schedule II controlled substance for a resident of an LTCF may be transmitted by the practitioner or practitioner's agent to the dispensing pharmacy by facsimile. In accordance with **21 CFR 1306.13**(b), a prescription for a schedule II controlled substance written for a patient in an LTCF may be filled by the pharmacy in partial quantities to include individual dosage units.

b. Request for Exemption for LTCFs

Several commenters requested that the DEA waive/exempt LTCFs from the more restrictive schedule II handling requirements with respect to HCPs. Some commenters asserted that such a waiver/exemption would be justified based on their assertion that there is a lower risk of misuse, abuse, and diversion of HCPs in an LTCF setting as compared to other settings. One nationwide professional association stated that:

[T]he long-term care setting has special and unique protections against diversion that are required by federal regulations and makes abuse and diversion very difficult and therefore, less likely to occur. * * * The regulatory standards and mandatory procedural checks in most cases make it difficult or impossible for any suspected abuse or diversion to occur over a sustained period of time. This makes diversion by staff difficult * * *. Other than anecdotal case here and there, there is no evidence that diversion is a systemic or frequent problem in SNF [skilled nursing facility] setting nor that the current proposed rule will correct [it].

This same commenter asserted that the "nursing home population is unlikely to be drug abusers" because "[t]heir health conditions often make them bed-bound or otherwise dependent on nurses for the administration of their medications."

DEA response. Nursing home residents take, on average, eight to ten medications per day.\13\ At least 17% of those medications are unused.\14\ Controlled substance medications are often stored and administered in LTCF settings as monthly punch cards (a.k.a. "bingo cards"), and liquid controlled substances are often dispensed in large-volume packaging.\15\ \16\ In addition, a 2011 report by the HHS Office of Inspector General found that almost all sampled nursing facilities employed one or more individuals with at least one criminal conviction, and nearly half of sampled nursing facilities employed five or more individuals with at least one conviction. Further, 44% of employees with convictions were convicted of crimes against property (e.g., burglary, shoplifting, writing bad checks).\17\ LTCFs are unique potential sources of diversion because the care provided to residents results in the accumulation of large amounts of controlled substances in a single, un-registered, relatively unsecure environment, where the disabled and elderly cannot defend themselves or adequately report what has happened.

\13\ The Lewin Group. CMS Review of Current Standards of Practice for Long-Term Care Pharmacy Services: Long-Term Care Pharmacy Primer. Prepared for: Centers for Medicare and Medicaid Services. December 30, 2004.

\14\ Gary Bazalo, MS, MBA, and Richard C. Weiss, MS, Managed Solutions, LLC. Measurement of Unused Prescription Drugs in Medicare Part D Nursing Stays. Jan. 12, 2011 at p. 6 (reporting survey results of consulting pharmacists conducted by the American Society of Consultant Pharmacists).

\15\ Marti A. Burton and Linda J. May Ludwig, Fundamentals of Nursing Care: Concepts, Connections & Skills 857 (2011); Norman V. Carroll, Ph.D., Michael T. Rupp, Ph.D., and David A. Holdford, Ph.D., Analysis of Costs to Dispense Prescriptions in Independently Owned, Closed-Door Long-Term Care Pharmacies, 20(3) JMCP 291 (2014) (76% of independently owned, closed-door pharmacies dispense 76% of doses to LTCFs in 28-31 day cycles).

\16\ Comment of American Society of Consultant Pharmacists on Docket No. DEA-316, "Disposal of Controlled Substances," Feb. 19, 2013 available at http://www.regulations.gov/#!documentDetail;D=DEA- 2012-0008-0144.

\17\ U.S. Department of Health and Human Services, Office of Inspector General, OEI-07-09-00110, Nursing Facilities' Employment of Individuals with Criminal Convictions (2011), available at http://oig.hhs.gov/oei/reports/oei-07-09-00110.pdf.

While focusing on the limited mobility of many residents in LTCFs as justification for why LTCFs should be able to adhere to less restrictive handling requirements for HCPs, commenters gave little consideration to potential diversion by employees, contractors, outside professionals, or visitors who may have access to their facilities. Direct access to controlled substances around a vulnerable population provides many opportunities for diversion of controlled substances, to the detriment of the LTCF

residents as well as the general public. For example, the Oregon Aging and People with Disabilities Division, alone, investigated 29 instances of drug theft at 17 different LTCFs in three counties, between 2009 and 2013.\18\ The average was 15.8 cases of medication theft per 1,000 beds/units, with the most often stolen products being narcotic

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painkillers--such as HCPs.\19\ These medication thefts occurred in both large nursing homes and small adult foster homes.\20\

\18\ Mac McLean, Drug Theft Affects Care, The Bulletin, Sept. 8, 2013, available at http://www.bendbulletin.com/news/1340250-153/drug-theft-affects-care.

\19\ Id.

\20\ Id.

Although not addressing LTCFs directly, the Mayo Clinic has reported on the diversion of drugs from within health care facilities and the threat to public health and safety such actions cause.\21\ Those risks included risk to patients receiving adulterated or contaminated drugs in place of the diverted drug as well as the risk of receiving substandard care from addicted employees.\22\ The Oregon investigations also included reports of having a patient's medication replaced with blood pressure medication--thus causing the combined risk of not receiving proper medication with the risk of overdose of another medication.

\21\ Keith H. Berge, et. al., Diversion of Drugs Within Health Care Facilities, a Multiple-Victim Crime: Patterns of Diversion, Scope, Consequences, Detection, and Prevention, 87(7) Mayo Clin. Proc. 674 (2012).

\22\ Id.

The most cursory of searches readily reveals multiple allegations reported in the news of thefts of controlled substances in nursing homes. For example, in 2012 six nursing home employees in Oklahoma were charged with operating a drug ring out of the facility for whom they were employed. Charges Filed in Nursing Home Drug Theft, KWGS News, July 5, 2012, available at http://publicradiotulsa.org/post/charges-filed-nursing-home-drug-theft. The Oklahoma Bureau of Narcotics (OBN) reported that 9,000 dosage units of controlled substances had been diverted from the facility by the nursing home employees, 8,400 of which involved hydrocodone. Press Release, Oklahoma Bureau of Narcotics and Dangerous Drugs Control (July 5, 2012) (on file with the Oklahoma Bureau of Narcotics); Oklahoma Nursing Home Employees Accused of Running Drug Ring: State v. Alexander, 15 No. 1 Westlaw Journal Nursing Home 4 (2012). The spokesman for OBN stated that employees would call in fraudulent prescriptions of hydrocodone for residents: "These residents had not been prescribed the Hydrocodone by doctors. There is no evidence that any resident was deprived of their legitimate medications. Evidence suggests some of the employees would personally use small amount of the diverted medication, but the majority of the fraudulent drugs were sold on the streets * * *." Id.

Criminal acts at LTCFs "often go undocumented, are seldom reported to law enforcement, and are rarely prosecuted."\23\ Even so, theft and diversion at LTCFs likely occurs on a local level, and when reported, are investigated and prosecuted at the local level. The diversion of controlled substances at LTCFs, whether wide-spread or discrete events, are a threat to the public health and safety, especially considering that such activity poses a real and direct threat to a vulnerable population. Public health and safety threats to disadvantaged, underrepresented, and historically vulnerable populations, including the elderly and mentally, physically, and emotionally/behaviorally disabled, disordered, or challenged, must be taken that much more seriously by those public bodies charged with protecting the public health and welfare. The DEA further notes that the misuse, abuse, and diversion of controlled substances, including pharmaceutical controlled substances, are not limited to any particular age group or functional level.

\23\ Wes Bledsoe, Criminal Offenders Residing in Long-Term Care Facilities, 2(3) J Forensic Nurs. 142 (2006).

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c. Transmission Method for Prescriptions

One commenter requested two changes to the transmittal methods for prescriptions: (1) Allow a prescribing practitioner to call in to the pharmacy an order for a limited supply, up to a 72 hour quantity, of a schedule II medication for an LTCF patient in an emergency situation, under existing regulations for schedule III-V controlled substances; and (2) Allow a practitioner's agent, acting on behalf of a prescribing practitioner, to call in the prescribing practitioner's verbal order for a small (72 hour) supply of a schedule II medication for an LTCF patient in an emergency situation, under existing regulations for schedule III-V controlled substances.

DEA response: The CSA requires that prescriptions for schedule II controlled substances be written, except in emergency situations as defined by the HHS. **21 U.S.C. 829**(a). Pursuant to **21 CFR 1306.11**(d), in the case of an emergency situation, a pharmacist may dispense a schedule II controlled substance upon receiving oral authorization from a prescribing individual practitioner provided that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period (dispensing beyond the emergency period must be pursuant to a written prescription signed by the prescribing individual practitioner).

The DEA recognizes the unique challenges and issues pertaining to handling and using controlled substances at LTCFs and has previously addressed these issues within the limits of the CSA.\24\ For example, a prescription for a schedule II controlled substance for an LTCF resident may be transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile. **21 CFR 1306.11**(f). In addition, a prescription for a schedule II controlled substance for an LTCF resident may be filled in partial quantities to include individual dosage units. **21 CFR 1306.13**(b).

\24\ E.g., "Preventing the Accumulation of Surplus Controlled Substances at Long Term Care Facilities," 66 FR 20833, Apr. 25, 2001; "Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies," 75 FR 61613, Oct. 6, 2010.

It is emphasized that a DEA registered practitioner may not delegate to a nurse, a pharmacist, or anyone else, his or her authority to make a medical determination whether to prescribe a particular controlled substance. Note that the practitioner remains responsible for ensuring that the prescription conforms in all essential respects to the law and regulations, **21 CFR 1306.05**(f). 75 FR 61613, 61614, Oct. 6, 2010. This requires the practitioner alone to determine on a prescription by prescription basis whether the prescription is supported by a legitimate medical purpose and that all the essential elements of the prescriptions are met.

d. E-Prescribing

One commenter requested that the DEA "promote the adoption of e- prescribing by requiring facilities and their respective pharmacy suppliers to allow physicians to electronically prescribe controlled substances consistent with the law and appropriate safeguards."

DEA response: This request is outside the scope of this rulemaking.

e. Emergency Kits

One commenter requested that the DEA "promote adoption of consistent and effective laws and policies across all states for the content and use of emergency kits (E-Kits) in the PA/LTC setting."

DEA response: This request is outside the scope of this rulemaking.

6. Abuse Prevention

Commenters raised concerns that, despite the scheduling of drugs, individuals will always find substances to abuse. These commenters argued that the proposed schedule II controls for

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HCPs will not address or stop the abuse of HCPs because other schedule II controlled substances such as oxycodone products are highly abused and diverted.

DEA response: The cycle of abuse between licit and illicit opioids, abuse of licit and illicit non-narcotic prescription drugs, and continued abuse of schedule I controlled substances such as LSD demonstrates that what individuals and communities are facing is not a problem specific to HCPs. Rather, it is an addiction problem. Heroin use and prescription drug abuse are both addictions that begin with use and are sustained and promoted through increased trafficking. This serious public health problem can be addressed by education, appropriate screening and treatment, recovery, support, and enforcement. These initiatives can be effective regardless of whether the problem is fed by heroin or prescription drugs, including HCPs, and the DEA supports all of these initiatives to address both prescription drug misuse and abuse and heroin use.

The problem of prescription drug abuse is fueled due to a combination of excessive prescribing, drug availability through friends and family, rogue pain clinics, practitioners who prescribe pharmaceutical controlled substances without legitimate medical purpose or outside the usual course of professional practice, pharmacies that dispense illegitimate prescriptions, and supply chain wholesalers and manufacturers that fail to provide effective controls and procedures to guard against diversion--all of which fuel illicit access at the expense of the public health and safety.

A balanced drug control strategy, one that includes strong enforcement, education, prevention, and treatment components, can make significant progress in protecting our nation from the dangers of drug abuse.

The DEA's enforcement responsibility as it pertains to drugs and other substances is clearly delineated in Federal law. Pursuant to **21 U.S.C. 811**(a), the CSA authorizes the DEA, under authority delegated by the Attorney General, to add to a schedule any drug or other substance if it is found that the drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by **21 U.S.C. 812**(b). As such, the legal system established by Congress specifically accounts for new substances to be added to the list of controlled substances without regard to the number of substances already controlled. See also 21 U.S.C. 812(a) ("Such schedules shall initially consist of * * *" (emphasis added)).

The dynamic structure constructed in the establishment of the schedules of controlled substances takes into consideration that the conclusions reached under each of the eight-factors specified under **21 U.S.C. 811**(c) may change over time. Scientific knowledge about a drug or substance grows, pharmacological knowledge increases, history and current patterns of abuse change, etc. The CSA scheduling protocols also take into account that new drug applications for drugs with abuse potential are submitted to and approved by the FDA as well as that clandestine chemists attempt to manipulate the molecular structures of controlled substances to create synthetic drugs that would have the same pharmacologic properties of a controlled drug, but not expose the chemist or distributor to criminal violations. The CSA, however does not only account for one-time scheduling determinations regarding the control of drugs and other substances. In addition to the initial control of drugs and other substances to schedules, the CSA likewise takes into account and provides for the transfer of a drug or other substance between schedules, or for a drug or other substance to be removed entirely from the schedules. 21 U.S.C. 811(a) and (b).

Nevertheless, the DEA disagrees that control of HCPs in schedule II will not decrease abuse of HCPs. Control of HCPs in schedule II will result in increased monitoring of these drugs as well as increased safeguards for legitimate prescriptions.

7. Diversion Prevention

Commenters also questioned whether moving HCPs to schedule II would reduce diversion of HCPs. These commenters argued that the proposed schedule II controls for HCPs will not address or stop the diversion of HCPs because other schedule II controlled substances such as oxycodone products are still diverted despite their schedule II status.

DEA response: The DEA disagrees that control of HCPs as schedule II controlled substances will not decrease their diversion. Control of HCPs into schedule II will result in increased monitoring of these drugs as well as increased safeguards for legitimate prescriptions.

8. Responsibilities of Pharmacists

The DEA received many comments, from pharmacists, physicians, ultimate users, and the general public, who were concerned that the increased administrative burden on pharmacists that might occur as a result of moving HCPs into schedule II would cause pharmacists to devote time to the administrative burdens rather than on patient counseling and safety. Commenters stated that the administrative burden would be greatly increased in the pharmacy setting because: separate prescriptions would have to be entered for every HCP; pharmacists would have to count the prescriptions, as technicians are not legally allowed to do so in some States; inventories would be required of all HCPs; and increased workload associated with recordkeeping requirements (i.e., DEA Form 222).

DEA response: The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination of whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**.

9. Requirements Applicable to Manufacturers and Distributors

a. Effective Date

Several of the comments submitted by members of industry (manufacturers, wholesale distributors, veterinary distributors, retail pharmacies), and/or trade associations representing them, focused on the timeframe for implementation of various handling requirements. A national trade association comprised of manufacturers and distributors of generic pharmaceutical products requested that the DEA "allow sufficient time for all parts of the supply chain to integrate the new requirements into their business operations." Similar requests were also posed by an individual manufacturer of HCPs, a wholesale distributor, and a retail pharmacy/mail pharmacy service provider, each who proposed a blanket six month delay before a final rule would go into effect. A national trade association comprised of distributors requested that the DEA allow at least 12 to 24 months, with opportunity for additional extension for individual registrants on an as needed basis, from the effective date of the final rule to allow for changes to facilities, policies and procedures. The national trade association requested that during the interim period registrants be allowed to continue to hold HCPs in cages rather than to be immediately required to place these items in vaults. Specifically, the association proposed that the DEA "[r]ecognize a registrant's compliance with the physical security requirements if the registrant has, by the implementation date of the storage

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requirements resulting from a rescheduling decision, submitted to the agency plans, blueprints, sketches, or other materials, including but not limited to signed contracts with contractors to implement any proposed physical security changes to the registrant's premises, and has otherwise been and continues to be in compliance with physical security requirements pursuant to [**21 CFR 1301.72**] for HCPs subject to this rescheduling decision as of the date prior to the effective date of a rescheduling decision." The national trade association additionally requested that the DEA provide specifics regarding the "process for submission of the materials demonstrating the vault construction plans" and how they might be able to "demonstrate compliance in lieu of vault construction completion."

DEA Response: In accordance with the Administrative Procedure Act, generally, DEA scheduling actions are effective 30 days from the date of publication of the final rule in the Federal Register. 5 U.S.C. 553(d). In order to ensure the continued availability of HCPs for legitimate medical use, while also ensuring they are not subject to misuse, abuse, and diversion, the DEA is establishing an effective date 45 days from the date of publication of this final rule. This 45-day period is a reasonable amount of time for registrants to comply with the handling requirements for a schedule II controlled substance and was established upon a full consideration of the totality of circumstances specific to HCPs.

The DEA understands that 45 days to implement all schedule II handling requirements may be perceived as short by some distributors. While the DEA acknowledges that the supply chain will need to plan and coordinate efforts, and may even need to temporarily modify existing ordering and inventory management practices, the DEA is required to consider the risk of diversion and risk to public health and safety of U.S. residents.

As summarized in the NPRM and the DEA presentation at the January 24, 2013, public DSaRM meeting, available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagmentadvisorycommittee/ucm346941.pdf, and discussed in detail in the supporting eight-factor analyses, HCPs are being abused with adverse effects both individually and to the public health and safety, accordingly, it should be placed into schedule II as soon as practicable. Prescription drug abuse refers to the intentional misuse of a medication by using more than medically indicated in order to feel the drug's psychoactive effects and/or using the drug in a manner that is not medically indicated. Prescription drug abuse has increased exponentially in the last 15 years and is the Nation's fastest growing drug problem. Factors including excessive prescriptions, drug availability through friends and family, Internet trafficking, rogue pain clinics, pharmacies that dispense illegitimate prescriptions, and failed safeguards by wholesalers and manufacturers to guard against diversion have all contributed to the prescription drug abuse problem.

The increase in prescription drug abuse has also been attributed to ease of obtaining the drug and the misconception that abusing prescription drugs is much safer than using and abusing street drugs. According to the 2012 Partnership Attitude Tracking Study (PATS), 43% of teenagers believe that prescription medications are "easier to obtain" than illegal drugs. In addition, the 2012 PATS also reported that 27% of teens believe that misusing or abusing prescription drugs is "safer" than using street drugs. Some of the increased demand for prescription opioid painkillers is from people who use them non- medically (using drugs without a prescription or just for the high they cause), sell them, or get them from multiple prescribers at the same time (CDC Vital Signs, July 2014, Opioid Painkiller Prescribing, Where You Live Makes a Difference).

According to the 2012 National Survey on Drug Use and Health (NSDUH), approximately 2.6% or 6.8 million people ages 12 and older are nonmedical users of prescription drugs. Abuse of opioid drugs, including HCPs, can lead to addiction, respiratory depression, and death. There were more than 16,000 deaths due to abuse of opioid drugs including HCPs in 2010. That is more than 1,333 people dying each month. According to the CDC, 38,329 people died from a drug overdose in the United States in 2010. Of these deaths, 22,134 people or 60% involved prescription drugs. Seventy-five percent of the prescription drug overdose deaths (16,651 people) were due to opioid drugs primarily containing oxycodone, hydrocodone, or methadone.

Abuse of prescription drugs is particularly alarming since data are strongly indicating that prescription opioid drug abuse can lead to heroin abuse.\25\ Specifically, data show that the population with the highest rate of heroin initiation was that population with prior nonmedical pain reliever use. The rate of heroin initiation among prior nonmedical pain reliever users was approximately 19 times greater than those who did not have such prior use. The rate of heroin initiation increased with increases in the frequency of past year nonmedical pain reliever use. Id.

\25\ SAMHSA, Center for Behavioral Health Statistics and Quality, Data Review, Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. August 2013 available at http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm.

The DEA has long held that increased heroin use is driven primarily by an increase in the misuse and abuse of prescription opioid drugs, particularly HCPs. The DEA's investigations indicate that the cost of prescription opioid drugs on the street may be as high as $80.00 per tablet and makes it difficult for teens and young adults to purchase drugs in support of their addiction. Therefore, abusers of prescription opioid drugs may resort to using heroin, a much cheaper alternative that produces similar euphoric effects, to keep the drug seeker/abuser from experiencing painful withdrawal symptoms. According to the most recent NSDUH, there were 335,000 heroin users in 2012, which is more than double the number in 2007 (161,000). In the decade from 2002 to 2011, the annual number of drug poisoning deaths involving heroin doubled, from 2,089 deaths in 2002 to 4,397 deaths in 2011.\26\

\26\ Hedegaard H, Chen L-H, and Warner M. Quick Stats: Rates of Drug Poisoning Deaths Involving Heroin, * by Selected Age and Racial/Ethnic Groups--United States, 2002 and 2011, MMWR 2014; 63:595.

HCPs are the most prescribed drug in the United States. Production of HCPs has increased from 15,359 kilograms in 1998 to 63,338 kilograms in 2012 (IMS, 2014). Increased production of HCPs is directly due to the increased prescription of these drugs to treat and alleviate pain. Even though there is legitimate use of HCPs, data indicate that a considerable population misuse HCPs. The National Poison Data System (NPDS) reported during the period of 2006-2012, that 45.4% of the total exposures to HCPs were considered intentional exposures, a surrogate to usage for abuse or misuse. The high percentage of HCPs for misuse supports that HCPs are contributing to prescription opioid drug abuse and may consequently lead to heroin abuse and death.

In order to prevent continued misuse, abuse and diversion, it is necessary to set an effective date for this scheduling action, including security and labeling requirements, with all reasonable haste.

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After careful consideration of the risk to the U.S. public health and safety related to the diversion and abuse of HCPs, the DEA believes the 45-day effective date is reasonable.

From the 2007 Economic Census, the DEA estimates that the inventory turnover ratio for the industry \27\ is approximately 11.3.\28\ The inventory turnover ratio represents the number of times the inventory sells (turns) in a year. The 11.3 inventory turnover ratio equates to an average of 32 days to sell inventory. The 11.3 turnover ratio is consistent with that of large distributors where financial information was publicly available and reviewed. The inventory turnover ratio is a reasonable estimate for the entire industry and all products under the circumstances. Publicly reviewed data show that about 85% of all revenues (an indirect indicator of dosage units moved) from drug distribution in the United States come from three public wholesalers, each with annual revenue in the billions. The DEA additionally notes that many regional and specialist pharmaceutical wholesalers have been acquired by the largest three distribution companies. Because the 32 days to sell inventory is an average based on industry-wide Census data, it is possible for an individual company and/or product line to experience a shorter or longer time to sell.

\27\ NAICS 424210--Drugs and druggists' sundries merchant wholesalers; Merchant wholesalers, except manufacturers' sales branches and offices.

\28\ The inventory turnover ratio of 11.3 was calculated by dividing the 2007 "cost of goods sold" for the industry of $280,481,051,000 by the average end-of-year 2006 and 2007 total inventories of $24,782,835,000.

Since HCPs are the most prescribed opioid drugs in the United States, with over 137 million prescriptions dispensed in 2013,\29\ the DEA expects distributors to continue to receive and distribute HCPs at high volume and with regularity; thus, anticipating shorter than average days to sell HCPs than the overall industry average ratio. In other words, the very high volume of sales indicates that HCPs are moving very quickly through the supply chain to meet demand, indicating high turnover and low inventory. However, to accommodate those manufacturers and distributors that have lower than average industry turnover ratio, the DEA is establishing an effective date of this final rule, including labeling and packaging requirements, 45 days from the date of publication. Based on the available information, and the lack of specific information regarding manufacturer and distributor inventory practices with respect to HCPs, the DEA believes this will provide a reasonable time for distributors to sell existing stock with pre-control labeling and packaging (C-III) and to stock inventory with post-control labeling and packaging (C-II).

\29\ IMS Health, National Sales Perspective TM (NSP).

The DEA anticipates manufacturers to begin developing inventory of HCPs with schedule II labels prior to the effective date of the rule to have stock ready to be distributed upon effect of this rule. The DEA estimates that 45 days is a reasonable amount of time for manufacturers and distributors to deplete existing inventory of HCPs. The packaging and labeling requirements for manufacturers and distributors do not apply to dispensers. Dispensers with HCPs in commercial containers labeled as schedule III may continue to dispense these HCPs after the implementation of this rule.

The DEA believes that HCPs labeled as C-III can be exchanged with HCPs containing new labels at nominal cost. The rule allows this exchange in a similar manner to the return of expired controlled substances authorized under existing regulations. Since manufacturers are expected to have ready-inventory of HCPs with new labels, exchanges are expected to occur without delay. In this rule, the DEA is allowing transfers of HCPs labeled as schedule III to be returned in exchange for HCPs labeled as schedule II without the requirement for procurement quota. Therefore, the DEA believes HCP manufacturers and distributors can reasonably make the necessary labeling changes and have inventory to meet the demands of customers.

The DEA acknowledges distributors may need to make some modifications to their inventory management system and operating procedures. However, these changes are expected to be procedural changes with only nominal impact on the burden created by the activities. For example, a distributor will need to receive, unpack, record the product in inventory, store, accept orders, and ship out to customers. These are all activities that occur regardless of the control status of HCPs. The anticipated changes may be a modification to the inventory management system and possible expansion of storage space (vaults).

The DEA has carefully considered the security requirements for compliance with this rule. As confirmed by the national trade association comprised of distributors, current distributors of HCPs are DEA registrants with existing controlled substance storage facilities that comply with DEA regulations. The DEA believes the DEA regulations provide flexibility that enables the supply chain to quickly implement the new rule without delay or significant cost.

Modifications necessary for physical security compliance will be a one-time modification primarily to provide for appropriate storage. The DEA understands that handlers of HCPs may also need to make modifications to their current security procedures for compliance. To a lesser extent, there may be necessary modifications to operating procedures, staff training, and amendments to suspicious order monitoring systems. However, due to the high diversion and abuse profile of HCPs, it is reasonably likely that most, if not all, manufacturers and distributors already provide controls and procedures to guard against theft and diversion of HCPs. That is, due to the high diversion potential of HCPs, most, if not all, manufacturers and distributors likely already have operating procedures (e.g., suspicious order monitoring systems, staff training) to guard against theft and diversion of HCPs, thereby necessitating minimal (if any) changes to these non-physical security controls. The DEA

believes that a 45-day period will provide handlers of HCPs a reasonable amount of time to implement any one-time modifications to comply with the DEA regulations. Registrants are familiar with the applicable security regulations, and already have systems in place with respect to other schedule II controlled substances. Accordingly, it is reasonable to revise operating procedures, amend monitoring systems, and train staff with respect to HCPs as schedule II controlled substances within the 45-day compliance timeframe.

The DEA has specifically chosen not to stagger implementation dates of handling requirements for the reasons stated herein. Also, different implementation dates leads to confusion and inconsistent application of the law, particularly with respect to rescheduling a drug from schedule III to schedule II. Schedule II and III substances are subject to different recordkeeping and reporting requirements, for example, and registrants would have difficulty keeping and maintaining records and inventories. Also, if one registrant category were to handle HCPs as schedule III controlled substances while another registrant category were to handle HCPs as schedule II controlled substances, it would be confusing (for the registrants and for enforcement authorities), particularly with respect to the relevant transaction records.

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The DEA strongly advises registrants to work closely with their local DEA office regarding submission of materials, storage containers, all applicable security requirements, and any necessary modifications due to compliance with this rule. **21 CFR 1301.71**(d); see also **21 CFR 1307.03**. After 45 days from the date of publication, HCPs will be subject to schedule II security requirements and must be handled and stored pursuant to **21 U.S.C. 821** and **823** and in accordance with **21 CFR 1301.71-1301.93**.

b. Distribution of C-III Labeled HCPs Post Implementation

The comments of a manufacturer, wholesale distributor, and national trade association comprised of distributors, each discussed their concerns about how commercial containers of HCPs labeled as "C-III" would be handled. The manufacturer requested that the DEA allow at least nine months from the date of issuance of the final rule for distribution of commercial products labeled as "C-III" in order to allow time for the supply chain to be restocked. This same company also requested that the DEA clarify the ability of reverse distributors and other registrants to continue to handle HCPs labeled as "C-III" for at least three months after the expiration date of the substance, in order to account for handling HCPs for purposes of destruction. The wholesale distributor wrote in favor of immediate implementation of the use of DEA Form 222, while allowing HCPs already labeled as C-III to be continuously distributed until depleted.

DEA response: For the reasons discussed in response to the previous comments, as of the effective date of the final rule, pursuant to **21 U.S.C. 821, 825**, and **958** (e) and in accordance with **21 CFR 1302.03**, manufacturers are required to print upon the labeling of each commercial container of HCPs they distribute the designation of HCPs as "C-II." It shall be unlawful for commercial containers of HCPs to be distributed downstream without bearing the label properly identifying them as schedule II controlled substances in accordance with **21 CFR part 1302**. As clearly stated in **21 CFR 1302.05**, "[a]ll labels on commercial containers of, and all labeling of, a controlled substance which either is transferred to another schedule or is added to any schedule shall comply with the requirements of **Sec. 1302.03**, on or before the effective date established in the final order for the transfer or addition." Accordingly, the DEA is requiring that commercial containers of HCPs distributed on or after 45 days from the date of publication of the final rule be labeled as "C-II" and be packaged in accordance with **21 CFR part 1302**.

A distribution of HCPs on or after the effective date of this final rule, is a distribution of a schedule II controlled substance, and a DEA Form 222 is required to be used to conduct the transfer in accordance with **21 CFR 1305.03**. A registrant may transfer commercial containers of HCPs labeled as "C-III" upstream on or after the effective date of the final rule, with utilization of a DEA Form 222 as required in accordance with 21 CFR 1305.03. Utilization of the DEA Form 222 ensures that schedule I and II controlled substances are accounted for, and allows for the detection and prevention of diversion.

Additionally, as discussed previously in more detail in the Economic Impact Analysis, the DEA believes that any manufacturer or distributor that requires more than 45 days to sell HCP inventory under normal circumstances can make minor modifications to ordering and stocking procedure for a transitional period to meet the established effective date. Distributors also have the option of returning excess stock of HCPs labeled as "C-III" to the manufacturer, or the manufacturer's authorized agent, as authorized by this final rule, or in accordance with 21 CFR 1307.12.

The DEA takes this opportunity to clarify that the regulation pertaining to labeling of commercial containers applies to distributions by manufacturers and distributors. The DEA does not regulate the labeling and packing of commercial containers of controlled substance downstream of distributors.

c. Exemption of Distributors and Manufacturers

A national trade association comprised of distributors and an individual manufacturer of HCPs requested that the DEA provide an exemption from the schedule II controlled substance security requirements for manufacturers and distributors of HCPs. Both commenters based this request on the assertion that manufacturers and distributors are not a documented significant source of diversion.

DEA response: Scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on purported sources of diversion. One of the primary functions of the DEA Diversion Control Program is to ensure that registrants are in compliance with the safeguards inherent in the CSA. This proactive approach is designed to identify and prevent the large scale diversion of controlled substances and listed chemicals into the illicit market. Manufacturers and distributors pose the greatest potential for large- scale diversion. As discussed in the final rule, "Controlled Substances and List I Chemical Registration and Reregistration Fees," there is great risk and grave consequences associated with the quantity and purity of controlled substances and/or chemicals with each manufacturer at this point in the closed system. 77 FR 15234, 15241, March 15, 2012. Accordingly, non-practitioners such as manufacturers and distributors must adhere to very stringent physical security requirements. The DEA has determined that there is a high potential for abuse of HCPs, and this, inter alia, requires that HCPs be controlled in schedule II. The physical security requirements applicable to schedule II controlled substances will provide secure controls to detect and prevent diversion of HCPs. Accordingly, the DEA declines to exempt manufacturers or distributors from the physical security requirements applicable to HCPs upon control in schedule II. However, the DEA encourages manufacturers and distributors to work closely with their local DEA office regarding submission of materials, storage containers, all applicable security requirements, and any necessary modifications due to compliance with this rule. **21 CFR 1301.71**(d); see also **21 CFR 1307.03**.

10. Economic Impact

a. Cost to Ultimate Users

Several commenters stated that the DEA had failed to fully take into account costs and impacts to ultimate users in its economic impact analysis.

DEA response: Scheduling decisions are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on the population it is intended or approved to treat, or potential impacts thereon. However, as

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discussed above, scheduling or rescheduling a drug does not hinder legitimate access to needed medication. For the reasons discussed earlier in this document, the DEA does not believe that there will be significant impacts, if any, on ultimate users associated with this rulemaking.

b. Cost of Physical Security

Several commenters suggested that it would cost millions of dollars for distributors and retail pharmacies to obtain new vaults or increase the size of their vaults to accommodate for the influx of HCPs. Another commenter suggested that only a limited number of firms can build vaults that meet the requirements of the DEA and because of this, constructing a vault would be time consuming and costly.

DEA response: Scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b). The DEA may not reschedule, or refuse to reschedule, a drug or other substance based on economic impacts.

Retail pharmacies are not required by the CSA or DEA regulations to place schedule II controlled substances in a vault or safe. In accordance with **21 CFR 1301.75** (b), pharmacies may disperse schedule II controlled substances throughout their stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances.

11. Proposed Alternatives

a. Establishment of a National Prescription Drug Monitoring Program (PDMP)

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Several commenters requested the implementation of a national prescription drug monitoring program (PDMP) either as an alternative to rescheduling HCPs, or possibly in addition thereto, as a means of curtailing doctor shopping and preventing abuse. For example, one commenter noted that "Despite broad consensus that prescribers and public health officials need these essential tools modernized to support clinical decision-making and identify state and regional patterns of abuse and diversion, state-based PDMPs continue to have limited financial resources and interoperability * * *." Another commenter stated that PDMPs "can be improved by creating incentives for inter-state connectivity, making data available in a more timely fashion and unifying standard submissions."

DEA response: One of the best ways to combat the rising tide of prescription drug abuse is the implementation and use of PDMPs. PDMPs help prevent and detect diversion and abuse of pharmaceutical controlled substances, particularly at the retail level where no other automated information collection system exists. PDMPs valuable tools for prescribers, pharmacists, and law enforcement agencies to identify, detect, and prevent prescription drug abuse and diversion.

The DEA supports and encourages the development and maintenance of PDMPs at the State level. Currently, 48 States have an operational PDMP (meaning collect data from dispensers and reporting information from the database to authorized users). One State has enacted legislation enabling the program to come online; Missouri has no state PDMP. As of February, 2014, only 16 States mandate usage of PDMP. Of those 16 States, 6 States mandate its usage in designated circumstances and 10 mandate its use in broader circumstances. Currently, 26 States have adopted the Interconnect platform for data sharing.

The DEA agrees with these commenters that the use of PDMPs is challenging across State lines because interconnectivity is limited. Interconnectivity or a nationwide system would help deter and detect drug traffickers and drug seekers, many of whom willingly travel hundreds of miles to gain easy access to unscrupulous pain clinics and physicians.

The Department has supported the development of PDMPs through the Harold Rogers Prescription Drug Monitoring grant program, distributing a total of over $87 million from FY 2002 to FY 2014, including $7 million in FY 2014. The purpose of this program is to enhance the capacity of regulatory and law enforcement agencies to collect and analyze controlled substance prescription data. It focuses on providing help for States that want to establish a PDMP or expand an existing PDMP. In 2012, the Department provided further policy guidance on data sharing efforts among State PDMPs, a critical aspect of the program.

b. Better Utilization of Currently Established State PDMPs Already in Existence

One commenter suggested that State monitoring systems should be used in a way to specifically identify usage of HCPs in the respective State. The commenter stated that this would allow each State to develop its own methods for handling the abuse of HCPs problem rather than making a nationwide rule rescheduling HCPs to schedule II. Another commenter suggested that practitioners should use State prescription monitoring programs more to prevent unnecessary refills and prescriptions, thereby preventing abuse. Another commenter suggested that States should be mandated to implement a PDMP if they don't already have one in existence.

DEA response: As mentioned above, States are free to implement their own PDMP. Moreover, States may customize their PDMP in a way that is most beneficial to that State. The States can do this so long as the laws governing the program do not conflict with the CSA, DEA regulations, or other federal law.

However, the DEA, as required by the CSA, has an obligation to control drugs or other substances that have a potential for abuse. Once the DEA controls a drug or substance, it must apply the provisions of the CSA to that newly controlled drug or substance. As stated, scheduling determinations are based on scientific determinations regarding the drug or other substance's potential for abuse, its potential for psychological and physical dependence, and whether the drug or other substance has a currently accepted medical use in treatment in the United States. **21 U.S.C. 812**(b).

c. Establishment of a List of "Vetted Patients"

One commenter suggested "that people who genuinely need the medication * * * be listed in the state monitoring system as patients who have been vetted and should be prescribed the medication without [schedule II] requirements." The commenter proposed that such vetting could be done on a six month renewal basis.

DEA response: The CSA does not prevent the States from enacting laws related to controlled substances or prevent States from creating stricter laws. See **21 U.S.C. 903**. However, States cannot create rules that are more relaxed than the CSA, and its implementing regulations, as this would be a conflict. See Id. Creating a list of vetted patients who do not have to comply with schedule II requirements would be in direct conflict with the CSA and schedule II prescription requirements. An individual practitioner must determine if an individual has a legitimate medical purpose to be issued a prescription for a controlled substance each time a prescription is issued. There is no

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mechanism to "vet" a patient in the CSA.

d. Monitoring and/or Enforcement

One commenter stated that "I believe more effort should go into the monitoring the narcotics registry and targeting [of] patients or doctors that are suspicious for abuse rather than trying to restrict the narcotics given." Another suggested to "vet the patients by 2 different doctor evaluations, vetting to extend for 6 months. Register the vetted patients in the state drug monitoring programs as 'OK' to obtain 90-day supplies. Patients not vetted get a very limited supply."

DEA response: The DEA actively pursues administrative action and civil and criminal prosecution of DEA registrants and individuals who divert controlled substances. One of the primary functions of the DEA Diversion Control Program is to ensure that all DEA registrants are in compliance with the safeguards inherent in the CSA. This proactive approach is designed to identify and prevent diversion of controlled substances and listed chemicals into the illicit market. Insofar as the issuance of and the filling of controlled substance prescriptions is concerned, prescribers and pharmacies, have an obligation to ensure that they do not prescribe or dispense controlled substances to individuals with no legitimate medical purpose for the controlled substance.

e. Change of Prescription Requirements While Retaining Schedule III Status

Several commenters suggested that the DEA change prescription requirements for HCPs while keeping them as schedule III controlled substances instead of transferring them to schedule II of the CSA. For example, some commenters suggested that subcategories be created for specific categories of practitioners, such as oncologists or emergency practitioners. Other commenters suggested that the DEA should limit the quantity of HCPs prescribed or number of refills authorized instead of rescheduling HCPs. As an example, one commenter suggested that any HCP prescriptions of 30 tablets and under should remain as a schedule III controlled substance and prescriptions for over 30 tablets of HCPs should be a schedule II controlled substance.

DEA response: The DEA cannot retain schedule III status for HCPs, as the DEA has determined that HCPs satisfy the criteria for control in schedule II of the CSA. **21 U.S.C. 812**(b).

The Assistant Secretary of the HHS provided a scientific and medical evaluation and a scheduling recommendation to control HCPs as a schedule II controlled substance. In accordance with **21 U.S.C. 811**(c), the DEA conducted its own analysis of the eight factors determinative of control. Besides published literature, various other data as detailed in the supporting documents were considered in making the scheduling determination for HCPs. Thus, the scheduling determination is based on a comprehensive evaluation of all available data as related to the required eight factors. The summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at http://www.regulations.gov under Docket No. DEA-389. Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that HCPs have an abuse potential and meets the requirements for schedule II controls under the CSA.

f. Education of Prescribing Practitioners

Several commenters suggested that prescribing practitioners should receive education about the problems of HCP abuse, addiction, and prevention of diversion rather than rescheduling HCPs.

DEA response: The DEA fully supports efforts by medical professionals, acting alone and as part of professional organizations, as well as industry associations, to educate members of their profession/industry on the risks associated with prescription opioid use and on ways to prevent misuse, abuse, and diversion of prescription opioid products. These efforts are an important and integral part of tackling the problem of prescription opioid abuse.

However, as recognized by the CDC, the United States is in the midst of a public health crisis regarding prescription painkiller overdose. Individuals, families, and society are suffering the effects of abuse and addiction. People are dying. In their 2011 report, the CDC estimated that 75 opioid-related deaths occur each day. T equates to over 27,000 people each year. As a society, America simply cannot afford to wait for self-initiated educational programs and measures by medical professionals and industry to solve the problem on their own. As acknowledged by commenters advocating solely for an educational approach, opioid consumption in the United States continues to increase despite self-initiated professional educational endeavors such as symposia and scientific articles.

One physician who wrote in support of rescheduling asserted that only a limited number of practitioners have paid attention to the warnings issued regarding the risk of addiction, overdose, and death associated with use of HCPs. It was this physician's belief that: "The opioid epidemic has mainly resulted from a large volume of

misinformed doctors failing to understand the risks and limited benefits of these drugs, especially for chronic noncancer pain, one of the most common reasons why patients seek medical care." This concern has been echoed by the HHS. The HHS has noted "Multiple studies have shown that a small percentage of prescribers are responsible for prescribing the majority of opioids." Behavioral Health Coordinating Committee, Prescription Drug Abuse Subcommittee, HHS. Addressing Prescription Drug Abuse in the United States: Current Activities and Future Opportunities. 2013. (internal citations omitted). The HHS points out, however, that "Providers who are not high-volume prescribers may also contribute to opioid abuse and overdose because of a lack of education and awareness about appropriate opioid prescribing * * *." The HHS additionally stated, "Even when sufficient information exists, studies show that some providers do not follow risk mitigation strategies even for patients known to be at high risk for abuse." Id. The physician- commenter asserted that "Upscheduling hydrocodone combination products will, at the very least, send a clear message to these providers that hydrocodone is a narcotic in the same class as oxycodone, morphine and heroin, which should be prescribed and refilled with the utmost of selectivity, caution and close patient follow-up."

The problem must be addressed both nationally and locally by using all available legal and social measures at hand. At the Federal level, this includes following the legal path directed by Congress to address issues of substance abuse and trafficking. As part of a comprehensive approach involving multiple Federal and State actors to address these concerns, Congress has charged the DEA with the responsibility to implement and enforce, to the fullest extent of the law, the requirements of the CSA. This includes ensuring that drugs and other substances are appropriately scheduled concordant with the factors for each schedule under **21 U.S.C. 812**(b).

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g. Education and Rehabilitation of Ultimate Users

Several commenters suggested that patient education and/or rehabilitation was the proper route to address abuse of HCPs rather than rescheduling.

DEA response: A multi-pronged approach, one that includes education, treatment, monitoring, and law enforcement is needed to combat this epidemic. The DEA supports all efforts to educate patients about the risks associated with use of substances with abuse potential. As discussed above, an analysis of the eight factors determinative of control demonstrates that HCPs warrant control II of the CSA. **21 U.S.C. 812**(b).

h. Strict Enforcement/Sanctions

Several commenters voiced an opinion that there should be strict enforcement against those that have diverted and illegally sold prescription HCPs. These commenters stated it would be a good idea to ban these offenders from receiving HCPs or reduce limits on how much HCPs an offender can receive. In addition, several commenters suggested tougher sanctions and enforcement should be applied to providers who are not lawfully practicing their trade rather than punishing those who are obeying the laws.

DEA response: The DEA mission is to implement and enforce the CSA and corresponding regulations to the fullest extent of the law. The DEA actively pursues administrative action and civil and criminal prosecution of DEA registrants and other individuals who divert controlled substances. One of the primary functions of the DEA Diversion Control Program is to ensure that registrants are in compliance with the safeguards inherent in the CSA. The DEA supports State and local law enforcement, and State professional and regulatory boards in their efforts to prevent diversion and enforce the controlled substances laws.

V. Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of HCPs. As such, the DEA is rescheduling HCPs as a schedule II controlled substance under the CSA.

VI. Determination of Appropriate Schedule

The CSA outlines the findings required to transfer a drug or other substance between schedules (I, II, III, IV, or V) of the CSA. **21 U.S.C. 811**(a); **21 U.S.C. 812**(b). After consideration of the analysis and rescheduling recommendation of the Assistant Secretary for Health of the HHS and review of available data, the Administrator of the DEA, pursuant to **21 U.S.C. 811**(a) and **21 U.S.C. 812**(b)(2), finds that:

1. HCPs have a high potential for abuse. The abuse potential of HCPs is comparable to the schedule II controlled substance oxycodone;

2. HCPs have a currently accepted medical use in treatment in the United States. Several pharmaceutical products containing hydrocodone in combination with acetaminophen, aspirin, other NSAIDs, and homatropine are approved by the FDA for use as analgesics for pain relief and for the symptomatic relief of cough and upper respiratory symptoms associated with allergies and colds; and

3. Abuse of HCPs may lead to severe psychological or physical dependence.

Based on these findings, the Administrator of the DEA concludes that HCPs warrant control in schedule II of the CSA. **21 U.S.C. 812**(b)(2).

VII. Requirements for Handling HCPs

Upon the effective date of this final rule, any person who handles HCPs will be subject to the CSA's schedule II regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engaging in research, conducting instructional activities, and conducting chemical analysis, of schedule II controlled substances, including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, conducts instructional activities with, or conducts chemical analysis with) HCPs, or who desires to handle HCPs, must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of October 6, 2014.

Security. HCPs are subject to schedule II security requirements and must be handled and stored pursuant to **21 U.S.C. 821** and **823**, and in accordance with **21 CFR 1301.71-1301.93** as of October 6, 2014.

Labeling and Packaging. All labels, labeling, and packaging for commercial containers of HCPs must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302** as of October 6, 2014, except with respect to exchanges for purposes of relabeling/ repackaging as provided below under "Quotas."

Quotas. A quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** is required in order to manufacture HCPs as of October 6, 2014. Registrants required to obtain an individual manufacturing quota shall not manufacture HCPs on or after October 6, 2014, unless an individual manufacturing quota is granted for such quantities of HCP to be manufactured. Registrants required to obtain a procurement quota shall not procure HCPs on or after October 6, 2014, unless a procurement quota is granted for such quantities of HCP to be procured.

Except, registrants authorized to manufacture schedule II and III controlled substances may relabel/repackage HCPs labeled as "CIII" or "C-III" without obtaining procurement quota for such activity, under the following conditions:

(1) The manufacturing activity occurs before December 8, 2014;

(2) if the manufacturer is relabeling/repackaging HCPs that were returned to the manufacturer, the manufacturer returns the same quantity and strength of HCPs labeled as "CII" or "C-II" back to the registrant that returned HCPs labeled as "CIII" or "C-III" to the manufacturer; and

(3) an invoice or the DEA Form 222 (whichever is applicable) records the transfer and reflects that the transfer occurred pursuant to the authority contained in this final rule.

For example, if before October 6, 2014, distributor A transfers 5 packages of 100-bottle 5/325 HCPs labeled as CIII/C-III to manufacturer B, solely for the purpose of relabeling, the invoice would reflect that the transfer occurred pursuant to the authority in this final rule. If the return occurs after October 6, 2014, the DEA Form 222 would reflect that the transfer occurred pursuant to the authority contained in this final rule. When the manufacturer distributes HCPs labeled as "CII" or C-II" back to the registrant that returned the HCPs labeled as "CIII" or "C-III," the manufacturer must return the same quantity and strength that was originally received for relabeling/repackaging. The DEA Form 222 will, again, reflect that the transfer occurred pursuant to the authority contained in this final rule.

In the above example, the manufacturer would not be required to obtain a procurement quota in order to relabel/repackage 5 packages of 100-bottle 5/325 HCPs, so long as

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manufacturer B subsequently transfers to distributor A 5 packages of 100-bottle 5/325 HCPs labeled as CII/C-II, unless the relabel/repackage activity occurs after December 8, 2014.

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Registrants may continue to return HCPs pursuant to 21 CFR 1307.12.

Inventory. Any person who becomes registered with the DEA on or after the effective date of the final rule must take an initial inventory of all stocks of controlled substances (including HCPs) on hand on the date the registrant first engages in the handling of controlled substances pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b) as of October 6, 2014.

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including HCPs) on hand every two years pursua **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records and Reports. Every DEA registrant must maintain records and submit reports with respect to HCPs pursuant to **21 U.S.C. 827** and **958**, and in accordan with **21 CFR parts 1304** and **1312** as of October 6, 2014. Each pharmacy with a modified registration under **21 U.S.C. 823**(f) that authorizes the dispensing o controlled substances by means of the Internet must submit reports to the DEA regarding HCPs pursuant to **21 U.S.C. 827** and in accordance with **21 CFR 1304** as of October 6, 2014.

Orders for HCPs. Every DEA registrant who distributes HCPs must comply with order form requirements, pursuant to **21 U.S.C. 821**, **828**, **871** and in accordance with **21 CFR parts 1305** and **1307** as of October 6, 2014.

Prescriptions. All prescriptions for HCPs must comply with **21 U.S.C. 829**(a) and must be issued in accordance with **21 CFR part 1306** and subpart C of **21 CFR part 1311** as of October 6, 2014. No prescription for HCPs issued on or after October 6, 2014 shall authorize any refills. Any prescriptions for HCPs that are issued before October 6, 2014, and authorized for refilling, may be dispensed in accordance with **21 CFR 1306.22-1306.23**, **1306.25**, and **1306.27**, if such dispensing occurs before April 8, 2015.

Importation and Exportation. All importation and exportation of HCPs must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and in accordance with **21 CFR part 1312** as of October 6, 2014.

Liability. Any activity involving HCPs not authorized by, or in violation of, the CSA or its implementing regulations, occurring as of October 6, 2014, is unlawful, and may subject the person to administrative, civil, and/or criminal action.

VIII. 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 performed "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 procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) 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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612) (RFA), has reviewed this rule, and by approving it, certifies that it will not a significant economic impact on a substantial number of small entities. The purpose of this rule is to place HCPs into schedule II of the CSA. No less restrictive measures (i.e., non-control or control in a lower schedule) would enable the DEA to meet its statutory obligation under the CSA.

HCPs are widely prescribed drugs for the treatment of pain and cough suppression. Handlers of HCPs primarily include manufacturers, distributors, exporters, pharmacies, practitioners, mid-level practitioners, and hospitals/clinics.\30\ It is possible that other registrants, such as importers, researchers, analytical labs, teaching institutions, etc., also handle HCPs. However, based on its understanding of its registrant population, the DEA assumes for purposes of this analysis that for all business activities other than manufacturers, distributors, exporters, pharmacies, practitioners, mid- level practitioners, and hospitals/clinics, that the volume of HCPs handled is nominal, and therefore de minimis to the economic impact determination of this rescheduling action.

\30\ For purposes of performing regulatory analysis, the DEA uses the definition of a "practitioner" as a physician, veterinarian, or other individual licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he/she practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, pharmacy, or hospital (or other person other than an individual). For the purposes of performing regulatory analysis, "mid-level practitioner" means an individual registered with the DEA as a "mid-level practitioner" but does not include practitioners as defined above. Examples of mid-level practitioners include, but are not limited to, health care providers such as nurse practitioners, nurse midwives, nurse anesthetists, clinical nurse specialists and physician assistants.

Because HCPs are so widely prescribed, for the purposes of this analysis, the DEA conservatively assumes all distributors, exporters, pharmacies, practitioners, mid-level practitioners, and hospitals/ clinics currently registered with the DEA to handle schedule III controlled substances are also handlers of HCPs. The DEA estimated the number of manufacturers and exporters handling HCPs directly from DEA records. In total, the DEA estimates that nearly 1.5 million controlled substance registrations, representing approximately 376,189 entities, would be affected by this rule.

The DEA does not collect data on company size of its registrants. The DEA used DEA records and multiple subscription-based and public data sources to relate the number of registrations to the number of entities and the number of entities that are small entities. The DEA estimates that of the 376,189 entities that would be affected by this rule, 366,351 \31\ are "small entities" in accordance with the RFA and Small Business Administration size

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standards. 5 U.S.C. 601(6); 15 U.S.C. 632.

\31\ The estimated break-down is as follows: 50 manufacturers; 4 exporters; 683 distributors; 50,774 pharmacies; and 314,840 persons registered as or employing practitioners/mid-level practitioners/ hospitals/clinics.

The DEA examined the registration, security (including storage), labeling and packaging, quota, inventory, recordkeeping and reporting, ordering, prescribing, importing, exporting, and disposal requirements for the 366,351 small entities estimated to be affected by the rule. The DEA estimates that only the physical securi requirements will have material economic impact and such impacts will be limited to manufacturers, exporters, and distributors. Many manufacturers and exporters are likely to have sufficient space in their existing vaults to accommodate HCPs. However, the DEA understands that some manufacturers, exporters, and distributo will need to build new vaults or expand existing vaults to store HCPs in compliance with schedule II controlled substance physical security requirements. Due to the uniqueness of each business, the DEA made assumptions based on research and institutional knowledge of its registrant community to quantify the costs associated with physical security requirements for manufacturers, exporters and distributors.

The DEA estimates there will be significant economic impact on 1 (2.0%) of the affected 50 small business manufacturers, and 54 (7.9%) of the affected 683 small business distributors. The DEA estimates no significant impact on the remaining affected 4 small business exporters, 50,774 small business pharmacies, or 314,840 small business practitioners/mid-level practitioners/hospitals/clinics.

In summary, 55 of the 366,351 (0.015%) affected small entities are estimated to experience significant impact, (i.e., incur costs greater than 1% of annual revenue) as a result of this rule being finalized. The percentage of small entities with significant economic impact is below the 30% threshold for all registrant business activities. The DEA's assessment of economic impact by size category indicates that the rule to reschedule HCPs as schedule II controlled substances will not have a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, the DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year * * *." Therefore, neither a Small Government agency Plan nor any other action is required under provisions of the UMRA 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). This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 amended as follows:

PART 1308--SCHEDULES 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.

Sec. 1308.13 [Amended]

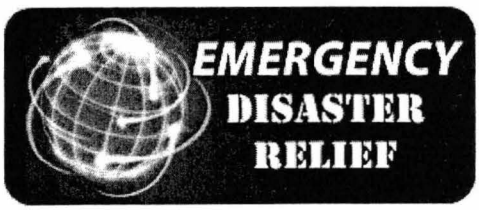
- 2. Amend **Sec. 1308.13** by removing paragraphs (e)(1)(iii) and (iv) and redesignating paragraphs (e)(1)(v) through (viii) as (e)(1)(iii) through (vi), respectively.

Dated: August 15, 2014.

Michele M. Leonhart,
Administrator.

[FR Doc. 2014-19922 Filed 8-21-14; 8:45 am]

BILLING CODE 4410-09-P



Rules - 2014

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-370]

Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV

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 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, or possess) or propose to handle alfaxalone and substances containing alfaxalone.

DATES: Effective Date: March 31, 2014.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, controlled substances are classified into 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 established by Congress are found at 21 U.S.C. 812(c), and the current list of all 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 [**21 U.S.C. 812**(b)] 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 the DEA. 28 CFR 0.104.

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 the Department of Health and Human Services (HHS),\1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action is based on a recommendation from the Assistant Secretary of the HHS and on an evaluation of all other relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle or propose to handle alfaxalone.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1995. In addition, because the Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations, for purposes of this document, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."

Background

Alfaxalone (5[alpha]-pregnan-3[alpha]-ol-11,20-dione, previously spelled "alphaxalone"), a substance with central nervous system (CNS) depressant properties, is a neurosteroid that is a derivative of 11-alpha-hydroxy-progesterone. On October 23, 2012, the Food and Drug Administration (FDA) published a final rule to approve a New Animal Drug Application (NADA, 141-342) for alfaxalone (Alfaxan[supreg]), as an intravenous injectable anesthetic, for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance of anesthesia with an inhalant anesthetic, in cats and dogs (77 FR 64715). Alfaxalone primarily

acts as an agonist at the gamma-aminobutyric acid (GABA) receptor-channel complex, with a mechanism of action at this site similar to that of barbiturates like phenobarbital (schedule IV) and methohexital (schedule IV), benzodiazepines such as diazepam (schedule IV) and midazolam (schedule IV), as well as the anesthetic agents

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propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol (schedule IV).

HHS and DEA Eight-Factor Analyses

On July 17, 2012, the Assistant Secretary of the HHS provided to the DEA a scientific and medical evaluation and scheduling recommendation entitled "Basis for th Recommendation to Control Alfaxalone in Schedule IV of the Controlled Substances Act." After considering the eight factors in **21 U.S.C. 811**(c), including consideration of the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that alfaxalone be controlled in schedule IV of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eight-factor analysis of alfaxalone pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket Number DEA-370) at www.regulations.gov under "Supporting and Related Material."

Determination to Schedule Alfaxalone

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV" which proposed placement of alfaxalone in schedule IV of the CSA. 78 FR 17895, March 25, 2013. The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by April 24, 2013. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before April 24, 2013.

Comments Received

The DEA received four comments on the proposed rule to schedule alfaxalone. Two commenters were in favor of controlling alfaxalone as a schedule IV controlled substance. One commenter was in favor of controlling alfaxalone as a schedule V controlled substance rather than a schedule IV controlled substance, and one commenter opposed the control of alfaxalone.

Support of the Proposed Rule:

Two commenters supported controlling alfaxalone as a schedule IV controlled substance. These commenters indicated support for controlling alfaxalone under the CSA based on the abuse potential of the substance. Because alfaxalone is indicated for use as a pre-anesthetic and anesthetic in cats and dogs, these commenters felt that the abuse potential was particularly high for persons with access to the substance in the medical field. One commenter noted that controlling alfaxalone as a schedule IV controlled substance is appropriate because it could be abused in a manner similar to other schedule IV CNS depressants. The commenters believe that controlling alfaxalone as a schedule IV controlled substance will provide the necessary controls to prevent its diversion.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

Opposition to the Proposed Rule:

Two commenters opposed the proposal to control alfaxalone as a schedule IV controlled substance.

Request Not to Control Alfaxalone:

One commenter opposed controlling alfaxalone at all and stated that alfaxalone does not have the same abuse potential as Xanax[supreg] (alprazolam) (schedule IV), Valium[supreg] (diazepam) (schedule IV), and other benzodiazepines. The commenter also stated that controlling alfaxalone under the CSA would make it difficult for veterinarians and animal surgeons to acquire the drug. Lastly, this commenter stated that alfaxalone is "unheard of outside of the veterinary community and does not have a 'black market' as do the other schedule IV drugs."

DEA Response: The DEA does not agree. 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." This scheduling action was initiated when the DEA received a scientific and medical evaluation and a scheduling recommendation to control alfaxalone as a schedule IV controlled substance from the Assistant Secretary of the HHS. In accordance with 21 U.S.C. 811(c), the DEA conducted its own analysis of the eight factors determinative of control or removal: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. The summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at www.regulations.gov under Docket Number DEA-370.

Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that alfaxalone has an abuse potential similar to other schedule IV drugs, including the benzodiazepines diazepam and midazolam, the barbiturates phenobarbital and methohexital, and also the anesthetic agents propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol. Alfaxalone also acts as an agonist at the gamma-aminobutyric acid (GABA) receptor-channel complex, with a mechanism of action at the site similar to that of benzodiazepines like diazepam(schedule IV) and midazolam (schedule IV). This mechanism of action is also similar to that of other schedule IV controlled substances, including barbiturates like phenobarbital and methohexital, and also anesthetic agents like propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol. It should be noted that alfaxalone's current exclusive use as a veterinary anesthetic drug and the asserted conclusion that there is no "black market" for the substance, do not negate its abuse potential and associated risk of diversion. The DEA and HHS analyses demonstrate that alfaxalone does have the potential for abuse and meets the necessary findings on potential for abuse, currently accepted medical use, and physical or psychological dependence for placement in schedule IV. Burdens associated with acquiring a substance as a result of control under the CSA are not relevant factors to the determination whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, the DEA disagrees with the unsupported statement that making alfaxalone a controlled substance would make it difficult for veterinarians and animal surgeons to

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acquire the drug. Several other anesthetic substances used by veterinarians and other practitioners are controlled under the CSA. All veterinarians and animal surgeons who are authorized by the State in which they practice to handle alfaxalone and who are registered with the DEA to dispense controlled substances may acquire alfaxalone once it is controlled. As discussed in the Regulatory Flexibility Analysis section of this document, currently 98% of DEA registrants (most of which are small businesses) are already authorized to handle schedule IV controlled substances.

Request to Control Alfaxalone as a Schedule V Substance:

One commenter stated that alfaxalone should be controlled as a schedule V controlled substance. This commenter stated that there was limited information available regarding alfaxalone's abuse. The commenter also stated that alfaxalone is a new introduction to the United States veterinary market, and controlling it in the least stringent schedule, schedule V, would minimize burdens on practitioners using it for legitimate purposes, while also imposing controls to account for its abuse potential.

DEA Response: The DEA does not agree. The DEA thoroughly reviewed the scientific and medical evaluation and the scheduling recommendation to control alfaxalone as a schedule IV controlled substance from the HHS.

Additionally, the DEA conducted its own analysis of the eight factors in accordance with **21 U.S.C. 811**(b) and made the findings required under **21 U.S.C. 812**(b) for the placement of alfaxalone in schedule IV. Based on the review of the HHS's evaluation and scheduling recommendation and all other relevant and available data, the DEA found that alfaxalone has an abuse potential similar to other schedule IV controlled substances, including the benzodiazepines diazepam and midazolam,

barbiturates phenobarbital and methohexital, and also the anesthetic agents propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010) and fospropofol.

While not relevant to the substance's schedule placement, the DEA does not agree with this commenter's concern that the requirements applicable to schedule IV controlled substances are more burdensome than the requirements applicable to schedule V controlled substances. There are only very minimal differences in handling requirements between schedule IV and schedule V controlled substances. Most importantly for purposes of responding to this comment, the physical security requirements for schedule IV and V controlled substances are the same. Also, under the CSA, schedule V controlled substances may be dispensed without a prescription, while schedule IV controlled substances may only be dispensed pursuant to a prescription. However, this distinction is of no consequence with regard to alfaxalone because alfaxalone cannot be prescribed by a veterinarian, nor may alfaxalone be dispensed by a pharmacist pursuant to a prescription. Federal law restricts this drug to use by or on the order of a licensed veterinarian (i.e., it may only be administered). 21 CFR 522.52; see also 21 CFR 514.8.

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of alfaxalone. As such, the DEA is scheduling alfaxalone 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 CSA outlines the findings required for placing 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 the HHS and review of all available data, the Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

(1) 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) has a low potential for abuse relative to the drugs or other substances in schedule III; the overall abuse potential of alfaxalone is comparable to the schedule IV controlled substances diazepam, midazolam, phenobarbital, methohexital, propofol (proposed to be controlled as a schedule IV substance, 75 FR 66195, Oct. 27, 2010), and fospropofol;

(2) 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) has a currently accepted medical use in treatment in the United States; alfaxalone was approved for marketing by the FDA as a veterinary anesthetic product for the induction and maintenance of anesthesia in cats and in dogs; and

(3) Abuse of 5[alpha]-pregnan-3[alpha]-ol-11,20-dione (alfaxalone) may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

Based on these findings, the Administrator of the DEA concludes that alfaxalone, including its salts, isomers, and salts of isomers, warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Alfaxalone

Upon the effective date of this final rule, any person who handles alfaxalone is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement in research, and conduct of instructional activities, of schedule IV controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) alfaxalone, or who desires to handle alfaxalone, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957** and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of March 31, 2014. Any person who currently handles alfaxalone and is not registered with the DEA must submit an application for registration and may not continue to handle alfaxalone as of March 31, 2014 unless the DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Security. Alfaxalone is subject to schedule III-V security requirements and must be handled and stored pursuant to **21 U.S.C. 821**, **823**, and **871**(b) and in accordance with **21 CFR 1301.71**-**1301.93**, as of March 31, 2014.

Labeling and Packaging. All labels and labeling for commercial containers of alfaxalone must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302**, as of March 31, 2014.

Inventory. Every DEA registrant who possesses any quantity of alfaxalone on the effective date of this final rule must to take an inventory of all stocks of alfaxalone on hand as of March 31, 2014, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d).

Any person who becomes registered with the DEA after March 31, 2014 must take an initial inventory of all stocks of controlled substances (including alfaxalone) on hand on the date the registrant first engages in the handling

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of controlled substances, pursuant to **21 U.S.C. 827** and **958** and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b).

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including alfaxalone) on hand every two years, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records. All DEA registrants must maintain records with respect to alfaxalone pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304**, **1307**, and **1312**, as of March 31, 2014.

Prescriptions. The DEA recognizes that alfaxalone is currently only approved as an injectable anesthetic that is administered to patients. The DEA also acknowledges that Federal law currently restricts alfaxalone to use by or on the order of a licensed veterinarian, and it may not be dispensed pursuant to a prescription. 21 CFR 522.52; see also 21 CFR 514.8. A "prescription" is defined as an order for medication which is dispensed to or for an ultimate user but does not include an order for medication which is dispensed for immediate administration to the ultimate user (e.g., an order to dispense a drug to a bed patient for immediate administration in a hospital is not a prescription). **21 CFR 1300.01**(b). However, any lawful prescriptions for alfaxalone or prescriptions for products containing alfaxalone must comply with **21 U.S.C. 829** and must be issued in accordance with **21 CFR parts 1306** and **1311 subpart C** as of March 31, 2014.

Importation and Exportation. All importation and exportation of alfaxalone must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and be in accordance with **21 CFR part 1312** as of March 31, 2014.

Criminal Liability. Any activity involving alfaxalone not authorized by, or in violation of, the CSA, occurring as of March 31, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

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

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612), has reviewed this final rule and by approving it certifies that it will n[redacted] have a significant economic impact on a substantial number of small entities. The purpose of this final rule is to place alfaxalone, including its salts, isomers, and s[redacted] of isomers, into schedule IV of the CSA. By this final rule, alfaxalone will remain in schedule IV unless and until additional scheduling action is taken to either trans[redacted] it between the schedules or to remove it from the list of schedules. See **21 U.S.C. 811** and **812**. No less restrictive measures (i.e., no control or control in schedu[redacted] enable the DEA to meet its statutory obligations under the CSA.

On September 6, 2012, the FDA approved for use in the United States one product containing alfaxalone, which will have FDA marketing exclusivity and patent protection for several years. Accordingly, the number of currently identifiable manufacturers, distributors, importers, and exporters for alfaxalone is extremely small. The manufacturer who obtained FDA approval for the sale of alfaxalone product in the United States is not considered a "small entity" in accordance with the RFA and Small Business Administration (SBA) size standards. Upon expiration of the exclusivity period, and more likely, the related patent, additional products containing alfaxalone may receive approvals from the FDA, and thus additional manufacturers, distributors, importers, and exporters will handle alfaxalone. Whether such manufacturers, distributors, importers, or exporters may qualify as small entities cannot be determined at this time.

There are currently approximately 1.5 million controlled substance registrations, representing approximately 381,000 entities. The DEA estimates that 371,000 (97%) of these entities are considered "small entities" in accordance with the RFA and SBA size standards. 5 U.S.C. 601(6) and 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the dispensing rates of new chemical entities, the DEA is unable to determine the number of small entities which might handle alfaxalone. However, because alfaxalone is a new chemical entity that is a veterinary anesthetic administered in veterinary settings and is not prescribed to ultimate users, the number of entities affected by the rule would be far fewer than the 381,000 entities represented by all DEA registrants. There are approximately 66,361 veterinarian practitioners and 23 veterinarian distributors (schedules III-V) registered with the DEA.

Despite the fact that the number of small entities possibly impacted by this rule could not be determined, the DEA concludes that they would not experience a significant economic impact as a result of this rule. The DEA estimates all anticipated alfaxalone handlers to be DEA registrants, and currently 98% of DEA registrants (most of which are small entities) are authorized to handle schedule IV controlled substances. Even assuming that all of these registrants were to handle alfaxalone (e.g., practitioners administer the substance), the costs that they would incur as a result of alfaxalone's scheduling would be nominal.

Registrants that dispense (e.g., administer) alfaxalone are expected to incur nominal additional security, inventory, and recordkeeping costs. These registered entities have already established and implemented the systems and processes required to handle schedule IV controlled

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substances and can easily absorb the costs of administering alfaxalone with nominal to no additional economic burden. For example, because DEA-veterinary practitioners are likely to already be schedule IV handlers, they already secure schedule II-V controlled substances in a securely locked, substantially constructed cabinet. See **21 CFR 1301.75**(b). Accordingly, the requirement to secure all controlled substances containing alfaxalone would not impose a significant economic burden upon DEA-registered practitioners as the infrastructure and materials for doing so are already in place. Labeling their products is routine and in the normal course of business of manufacturers. The DEA therefore assumes that the cost of compliance with **21 CFR part 1302** as a result of this final rule is nominal. Correspondingly, the DEA estimates that the cost of the labeling and packaging requirements of this final rule is nominal for the authorized manufacturer. Accordingly, compliance would not require significant additional manpower, capital investment, or recordkeeping burdens.

Because of these facts, this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sect[redacted] of $100,000,000 or more (adjusted for inflation) in any one year * * * ." Therefore, neither a Small Government Agency Plan nor any other action is required unde[redacted] provisions of UMRA 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. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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 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. Amend **Sec. 1308.14** by redesignating paragraphs (c)(1) through (c)(53) as paragraphs (c)(2) through (c)(54) and adding new paragraph (c)(1) to read as follows:

Sec. 1308.14 Schedule IV.

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(c) * * *

(1) Alfaxalone—(2731)

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Dated: February 21, 2014.

Michele M. Leonhart,
Administrator.

[FR Doc. 2014-04332 Filed 2-26-14; 8:45 am]

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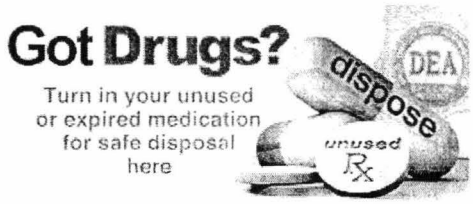

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[Federal Register Volume 79, Number 167 (Thursday, August 28, 2014)]
[Rules and Regulations]
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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-381]

Schedules of Controlled Substances: Placement of Suvorexant into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Deputy Administrator of the Drug Enforcement Administration (DEA) places the substance [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess), or propose to handle suvorexant.

DATES: Effective Date: September 29, 2014.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152, Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, and are collectively referred to as the "Controlled Substances Act" or the "CSA" for the purpose of this action. **21 U.S.C. 801-971**. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), **parts 1300 to 1321**. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the substance may cause. **21 U.S.C. 812**. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." The Attorney General has delegated this authority to the Administrator of the DEA, 28 CFR 0.100, who in turn has redelegated that authority to the Deputy Administrator of the DEA. 28 CFR part 0, appendix to subpart R.

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 Health and Human Services (HHS); \1\ or (3) on the petition of any interested party. **21 U.S.C. 811**(a). This action imposes the regulatory controls and administrative, civil, and criminal sanctions of schedule IV controlled substances on persons who handle or propose to handle suvorexant.

\1\ As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations.

Background

Suvorexant ([(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone), also known as MK-4305, is a new chemical entity developed for the treatment of insomnia. Suvorexant is a novel, first in class, orexin receptor antagonist with a

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mechanism of action distinct from any marketed drug. It acts via inhibition of the orexin 1 (OX1) and orexin 2 (OX2) receptors. In pharmacological activity studies, suvorexant functioned as an antagonist as demonstrated by its ability to block agonist-induced calcium (Ca\2+\) release. The U.S. Food and Drug Administration (FDA) approved the new drug application for suvorexant on August 13, 2014.

DEA and HHS Eight Factor Analyses

On June 27, 2013, the HHS provided the DEA with a scientific and medical evaluation document prepared by the FDA entitled "Basis for the Recommendation to Place Suvorexant in Schedule IV of the Controlled Substances Act." After considering the eight factors in **21 U.S.C. 811**(c), including consideration of the substance's abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that suvorexant be controlled in schedule IV of the CSA under **21 U.S.C. 812**(b). In response, the DEA conducted its own eightfactor analysis of suvorexant pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket Number DEA-381) at http://www.regulations.gov under "Supporting and Related Material."

Determination to Schedule Suvorexant

After a review of the available data, including the scientific and medical evaluation and the scheduling recommendation from the HHS, the Deputy Administrator of the DEA published in the Federal Register a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of Suvorexant into Schedule IV" which proposed placement of suvorexant in schedule IV of the CSA. 79 FR 8639, Feb. 13, 2014. The proposed rule provided an opportunity for interested persons to file a request for hearing in accordance with DEA regulations by March 17, 2014. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before March 17, 2014.

Comments Received

The DEA received five comments on the proposed rule to schedule suvorexant. Two commenters supported controlling suvorexant as a schedule IV controlled substance. One commenter opposed the control of suvorexant, one commenter did not articulate an official position, and one commenter was in favor of controlling suvorexant as a schedule III controlled substance, rather than a schedule IV controlled substance.

Support for the Proposed Rule

Two commenters supported controlling suvorexant as a schedule IV controlled substance. These commenters indicated support for controlling suvorexant under the CSA based on the abuse potential of the substance. The commenters noted that controlling suvorexant as a schedule IV controlled substance is appropriate because it is similar to zolpidem (schedule IV), while one commenter stated that suvorexant produces fewer adverse effects than zolpidem. The commenters believe that controlling suvorexant as a schedule IV controlled substance will provide the necessary controls to prevent its diversion.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

Opposition to the Proposed Rule

Two commenters opposed the proposal to control suvorexant as a schedule IV controlled substance, and one commenter did not articulate an official position but expressed concern about the side effects of suvorexant.

Request Not To Control Suvorexant

One commenter opposed controlling suvorexant because they believed that there was a lack of strong scientific evidence that suvorexant has been abused, and the comparison of suvorexant with zolpidem (schedule IV) is incorrect due to each compound eliciting its effects via different mechanisms of action. The commenter was also concerned that controlling suvorexant will make it more difficult for patients to obtain the substance once it is approved by the FDA.

DEA Response: The DEA does not agree. Suvorexant is a novel, first in class, new chemical substance and information on actual abuse data is not currently available. The legislative history of the CSA addresses the assessment of a new drug's potential for abuse,\2\ and data from clinical studies investigating the abuse potential for suvorexant suggests that its effect is similar to zolpidem (schedule IV). Similarly, while the mechanism of action for suvorexant is distinct from any currently marketed drug for insomnia, human abuse potential studies demonstrated that suvorexant produced effects that were indistinguishable from zolpidem (schedule IV).

\2\ The legislative history of the CSA provides that a substance may have a potential for abuse if: "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." Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444 (1970); as reprinted in 1970 U.S.C.C.A.N. 4566, 4601.

Burdens associated with acquiring a substance as a result of control under the CSA are not relevant factors to the determination whether a substance should be controlled or under what schedule a substance should be placed if it is controlled. See **21 U.S.C. 811** and **812**. Nonetheless, the DEA disagrees with the unsupported statement that making suvorexant a controlled substance will make it difficult for ultimate users to legally acquire the substance once it is approved by the FDA. If a DEA-registered practitioner lawfully prescribes suvorexant to treat a medical condition, it may be dispensed on the basis of an oral or written prescription. **21 CFR 1306.04**(a), **1306.21**.

Request To Control Suvorexant as a Schedule III Substance

One commenter had multiple concerns regarding the placement of suvorexant in schedule IV. The commenter believed that further studies on minimal levels of effective suvorexant doses should be conducted to reduce the risks of driving accidents. The commenter also expressed concern about the FDA's statement that while effective, suvorexant is unsafe at various doses. This commenter believed that due to lack of conclusive findings, suvorexant should be categorized as a schedule III controlled substance for "safety and precautionary purposes" since it is a novel, first in class, new substance.

Another commenter, who did not articulate a specific position, expressed concern that the side effects produced by suvorexant were similar to the effects of sleep deprivation, including cognitive and psychomotor impairment.

DEA Response: The concerns about the limited research on minimal levels of effective suvorexant doses and the side effects of suvorexant and sleep deprivation, along with the statement that suvorexant is unsafe at various doses, are outside the scope of the DEA's scheduling authority. As part of the new drug approval process, the HHS

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provides scientific and medical evaluations of a drug or other substance to ensure that it is safe and effective for its intended use. This process is completely separate from the DEA's proceedings to control such drug or other substance. **21 U.S.C. 811**.

The DEA does not agree that suvorexant should be controlled as a schedule III controlled substance. 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 [**21 U.S.C. 812**(b)] for the schedule in which such drug is to be placed * * *." This scheduling action was initiated when the DEA received a scientific and medical evaluation and a scheduling recommendation to control suvorexant as a schedule IV controlled substance from the Assistant Secretary of the HHS. In accordance with 21 U.S.C. 811(c), the DEA conducted its own analysis of the eight factors determinative of control or removal: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. The summary of each factor as analyzed by the DEA and the HHS, and as considered by the DEA in this scheduling action, was provided in the proposed rule. Both the DEA and the HHS analyses have been made available in their entirety under "Supporting and Related Material" of the public docket for this rule at http://www.regulations.gov under Docket Number DEA-381.

There is evidence that suvorexant has a potential for abuse comparable to zolpidem (schedule IV), and like zolpidem, suvorexant has a low potential for abuse relative to the drugs or other substances in schedule III. Suvorexant was compared to zolpidem in human studies of recreational sedative users to measure its abuse potential relative to that of a sedative-hypnotic in schedule IV. The abuse potential of suvorexant (40, 80 and 150 mg) relative to zolpidem (15 and 30 mg) and placebo was evaluated via a visual analog scale VAS, with results demonstrating that the effects of suvorexant were statistically indistinguishable from zolpidem. The results of the human abuse potential study suggest that suvorexant and zolpidem produce similar reinforcing effects and have a similar potential for abuse. In addition, preclinical

studies demonstrated that suvorexant (10, 20, 30 and 60 mg/kg) dose dependently reduced locomotor activity in rats, similar to other sedative drugs including zolpidem (schedule IV). Based on the review of the HHS evaluation and scheduling recommendation and all other relevant data, the DEA found that suvorexant has an abuse potential similar to other schedule IV drugs, including zolpidem (schedule IV).

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of suvorexant. As such, the DEA is scheduling suvorexant 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 CSA outlines the findings required for placing 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 the HHS and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

(1) [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) has a low potential for abuse relative to the drugs or other substances in schedule III. The overall abuse potential of suvorexant is comparable to the schedule IV controlled substance zolpidem;

(2) [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) has a currently accepted medical use in treatment in the United States. Suvorexant was approved for marketing by FDA as a treatment for insomnia; and

(3) Abuse of [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (suvorexant) may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III. The potential for psychological dependence is similar to that of zolpidem (schedule IV).

Based on these findings, the Deputy Administrator of the DEA concludes that suvorexant, including its salts, isomers, and salts of isomers, warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Suvorexant

Upon the effective date of this final rule, any person who handles suvorexant is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, engagement in research, and conduct of instructional activities, of schedule IV controlled substances including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) suvorexant, or who desires to handle suvorexant, must be registered with the DEA to conduct such activities, pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312** as of September 29, 2014. Any person who currently handles suvorexant and is not registered with the DEA must submit an application for registration and may not continue to handle suvorexant as of September 29, 2014 unless the DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

Security. Suvorexant is subject to schedule III-V security requirements and must be handled and stored pursuant to **21 U.S.C. 821**, **823**, and **871**(b) and in accordance with **21 CFR 1301.71**-**1301.93**, as of September 29, 2014.

Labeling and Packaging. All labels, labeling, and packaging for commercial containers of suvorexant must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302**, as of September 29, 2014.

Inventory. Every DEA registrant who possesses any quantity of suvorexant on the effective date of this final rule must take an inventory of all stocks of suvorexant on hand as of September 29, 2014, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (d).

Any person who becomes registered with the DEA after September 29, 2014

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must take an initial inventory of all stocks of controlled substances (including suvorexant) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958** and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**(a) and (b).

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including suvorexant) on hand every two years, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Records. All DEA registrants must maintain records with respect to suvorexant pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304**, **1307**, and **1312**, as of September 29, 2014.

Prescriptions. All prescriptions for suvorexant or products containing suvorexant must comply with **21 U.S.C. 829**, and be issued in accordance with **21 CFR part 1306** and subpart C of **21 CFR part 1311** as of September 29, 2014.

Importation and Exportation. All importation and exportation of suvorexant must be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and be in accordance with **21 CFR part 1312** as of September 29, 2014.

Liability. Any activity involving suvorexant not authorized by, or in violation of, the CSA, occurring as of September 29, 2014 is unlawful, and may subject the person to administrative, civil, and/or criminal proceedings.

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 drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Executive Order 13175

This rule does not have tribal implications warranting the application of Executive Order 13175. The rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601-612, has reviewed this final rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this final rule is to place suvorexant, including its salts, isomers and salts of isomers, into schedule IV of the CSA. No less restrictive measures (i.e., non-control, or control in schedule V) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Suvorexant is a new molecular entity which has not yet been marketed in the United States or any other country. Accordingly, the number of currently identifiable manufacturers, importers, and distributors for suvorexant is extremely small. The publicly available materials also specify the readily identifiable persons subject to direct regulation by this final rule. Based on guidelines utilized by the Small Business Administration (SBA), the suvorexant manufacturer/ distributor/importer was determined not to be a small entity. Once generic equivalents of suvorexant are developed and approved for manufacturing and marketing, there may be additional manufacturers, importers, and distributors of suvorexant, but whether they may qualify as small entities cannot be determined at this time.

There are approximately 1.5 million controlled substance registrations that represent approximately 381,000 entities (which include businesses, organizations, and governmental jurisdictions). The DEA estimates that 371,000 (97%) of these entities are considered "small entities" in accordance with the RFA and SBA size standards. 5 U.S.C. 601(6); 15 U.S.C. 632. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the dispensing rates of new molecular entities, the DEA is unable to determine what number of these 371,000 small entities might handle suvorexant.

Despite the fact that the number of small entities possibly impacted by this rule could not be determined, the DEA concludes that they would not experience a significant economic impact as a result of this final rule. The DEA estimates all anticipated suvorexant handlers to be DEA registrants and currently 98% of DEA registrants (most of which are small entities) are authorized to handle schedule IV controlled substances. Registrants that handle suvorexant are expected to incur nominal additional security, inventory, and recordkeeping costs. These registered entities are likely to have already established and implemented the systems and processes required to handle schedule IV controlled substances and can easily absorb the costs of handling suvorexant with nominal to no additional economic burden. For example, because DEA-registered pharmacies and institutional practitioners are likely to already be schedule IV handlers, they may secure schedule II-V controlled substances by dispersing such substances throughout the stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances. Additionally, because other DEA registrants who will handle suvorexant are likely to already be schedule IV handlers, they already should have existing secure storage areas for schedule II-V controlled substances, which we assume would be able to accommodate any new stocks of suvorexant. See **21 CFR 1301.75** (b), **1301.72**(b). Accordingly, the requirement to secure all controlled substances containing suvorexant would not impose a significant economic burden upon DEA-registered practitioners as the infrastructure and materials for doing so are already in place. The DEA therefore assumes that the cost of compliance with **21 CFR 1301.71-1301.77** as a result of this final rule is nominal.

Correspondingly, because DEA-registered manufacturers, distributors,

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and importers must label and package all schedule II-V controlled substances in accordance with **21 CFR part 1302**, the requirement to label and package all controlled substances containing suvorexant in accordance with 21 CFR part 1302 would not impose a significant economic burden upon DEA-registered manufacturers, distributors, and importers as the infrastructure and materials for doing so would already be in place. Accordingly, compliance with 21 CFR part 1302 would not require significant additional manpower, capital investment, or recordkeeping burdens.

Because of these facts, this final rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), the DEA has determined and certifies pursuant to UMRA that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year . . . ." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA 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. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). 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 for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; 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. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

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, the DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

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

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

- 2. Amend **Sec. 1308.14** by redesignating paragraphs (c)(49) through (c)(54) as (c)(50) through (c)(55) and adding new paragraph (c)(49) to read as follows:

Sec. 1308.14 Schedule IV.

* * * * *

(c) * * *

(49) Suvorexant 2223

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Dated: August 21, 2014.

Thomas M. Harrigan,
Deputy Administrator.

[FR Doc. 2014-20515 Filed 8-27-14; 8:45 am]

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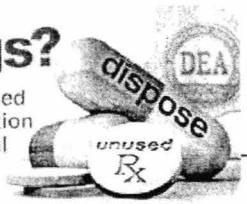

Applications, Tools & Resources
CMEA Required Training & Self-Certification
Quota Applications

ABOUT US

Program Description
Customer Service Plan
DEA Forms & Applications
Mailing Addresses
Meetings & Events
What's New

ING

ARCOS
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Chemical Import/Export Declarations
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Cases Against Doctors
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Drug and Chemical Information
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Title 21 Code of Federal Regulations
Title 21 USC Codified CSA

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#2

SB 2100

Charlene Keller
Forensic Scientist
March 10, 2015

The designer drug market is still changing and new substances are still being created to evade legislation previously passed, but not nearly to the scale that we were dealing with a few years ago. Last legislative session I told you about the three main groups of designer drugs: Synthetic Cannabinoids – sold as incense or potpourri giving users a high similar to THC (Marijuana), Substituted Cathinones – sold as Bath Salts producing central nervous system stimulant effects, and Hallucinogens – producing effects similar to LSD. Legislation was passed for each of these groups using a chemical class approach which defined a core molecular structure and listed possible substitutions and modifications. These laws have helped in the fight against designer drugs as a large number of compounds and their derivatives are controlled in our state, and we have noticed a large decrease in the amount being submitted to the ND Crime Lab. The good news is our current laws for the Substituted Cathinones (Bath Salts) and Hallucinogens is sufficient, and no changes or additions need to be made at this time. DEA has recently specifically listed some of these compounds into the federal code but these were already included in our state law (along with their listed derivatives). This shows that our approach is working and is proactive. The synthetic cannabinoids group is where some changes are required, as new derivatives continue to show up that are not included in our current legislation. The number of synthetic cannabinoid samples submitted to lab has greatly decreased. But when a synthetic cannabinoid sample is identified, there is a good chance it is no longer one of the previously controlled compounds but rather one belonging to a new generation of synthetic cannabinoid compounds.

This session, the proposed changes include adding three new groups under the synthetic cannabinoid section. These group definitions are more comprehensive and therefore would replace four of the existing cannabinoid groups. The first new group, Indole Carboxaldehydes, replaces the following current groups in the century code: Naphthoylindoles, Phenylacetylindoles, Benzoylindoles, and Tetramethylcyclopropanoylindoles. The definition includes all of the compounds in the four replaced groups and additionally includes compounds not covered in the previous definitions. The other two new groups would include newer compounds the forensic community has identified in casework and would include a few of the compounds that were currently listed in the 'others specifically named' section. To summarize, currently there are eight defined cannabinoid groups with nine compounds listed specifically. With the proposed changes, the new legislation would have seven cannabinoid groups with four compounds specifically named. The three new defined core structure groups with listed substitutions is more comprehensive and includes more compounds, including the new generation of compounds identified in forensic case work.

North Dakota has some of the best all inclusive laws encompassing hundreds of compounds when you compare our law to some other states. The laws specifically define what is and what is not covered in the definitions of the groups and other states have followed our lead with some of the definitions. It may seem like it is a never ending battle with designer drugs, but all we can do is to stay on top of what is currently being identified in the forensic community, and modify our laws accordingly. The laws are working and have made a difference. This session we are just proposing some fine tuning to the synthetic cannabinoid laws to make them more inclusive of past and present compounds.