Significant Legislative Rule Analysis (SA)
WAC 246-887-170,
Scheduling Carisoprodol

Section 1. Proposed Schedule IV Status for Carisoprodol (Soma)

The proposed rule categorizes the legend drug carisoprodol as a Schedule IV controlled substance of the Uniformed Controlled Substances Act. Scheduling moves a legend drug (i.e., a standard prescription drug) to a classification that recognizes that the drug has an actual or relative potential for abuse.

The Controlled Substance Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against the abuse of drugs and other substances. Federal and state governments have independent authority to add, delete, or reschedule substances as scheduled drugs. RCW 69.50.201 grants the Washington State Board of Pharmacy (Board) the authority to list a substance if they find that the drug has an actual or relative potential for abuse. The Board must assess eight factors when considering scheduling a legend drug. Thirteen states have scheduled carisoprodol as a schedule IV substance.

<u>Background Information on Carisoprodol</u>
Carisoprodol is a central acting muscle relaxant that prescribers use in combination with rest, physical therapy, and other treatments for the relief of acute, painful musculoskeletal conditions. Soma®, the brand name for carisoprodol, has been marketed since 1959. Other carisoprodol products available include carisoprodol compound (with aspirin) and carisoprodol codeine. There are seven other muscle relaxant drugs that are commonly prescribed for patients by health care providers. These other muscle relaxants provide similar treatment effects, but only carisoprodol has been shown to have the risks of abuse, addiction, intoxication, and psychomotor impairment.

There are numerous reports of carisoprodol abuse in the medical literature (1-9). Commercially prepared drugs, including carisoprodol, are the focus of drug abuse prevention efforts in addition to illicit drugs. Those who abuse carisoprodol commonly take it with other drugs such as alcohol, benzodiazepines, and opiates. The Washington State Patrol lab found that carisoprodol was one of the central nervous system depressant drugs commonly found in fatally injured drivers (10). National drug abuse tracking systems, such as the Drug Abuse Warning Network (DAWN) (11, 12), have been collecting drug data associated with drug abuse. The number of reported cases where carisoprodol is present has increased since 1994.

In 2000, the Federal Drug Enforcement Agency (DEA) began collecting data on the drugs secured in law enforcement operations across the country. These drugs are analyzed by federal, state and local forensic laboratories. The DEA has found carisoprodol among the top 25 drugs secured every year since 2000 (13,14). See Appendix A Underlying Cause of Death table.

Students from the University of Washington School of Pharmacy brought the issue of carisoprodol abuse to the attention of the Board. The students researched carisoprodol abuse concerns as a project for their Pharmacy Law class. They found that the concerns about carisoprodol abuse met the legal criteria in RCW 69.50.201 to schedule a drug. Subsequently, the students filed a petition for rulemaking with the Board to place carisoprodol into Schedule IV. See Appendix B Student Petition.

The Board found the student information compelling enough to direct Department of Health staff to assess if carisoprodol should be scheduled. The Washington State Pharmacy Association surveyed Washington State practicing pharmacists to compile their experiences with carisoprodol dispensing. The pharmacists cited numerous issues with patients seeking early medication refills, large amounts of carisoprodol, and obtaining prescriptions from multiple providers. They also have seen that providers are increasingly taking measures to limit amounts of carisoprodol prescribed, for example, by the use of patient contracts. Based upon their experience, 98% of the pharmacists thought carisoprodol is frequently abused by patients and should be scheduled (17). The University of Washington School of Pharmacy surveyed hundreds of physicians to gauge their opinion on the abuse potential of carisoprodol and asked them how their practice would change if carisoprodol is scheduled (18). Many of the physicians did not prescribe carisoprodol, or prescribe just a few prescriptions per month. Nearly 70% of physicians said that they would not change the amount of carisoprodol they prescribe if carisoprodol moved to schedule IV.

Based upon information collected by Department of Health staff, coupled with all of the input received from physicians and pharmacists, the Board finds that carisoprodol clearly has a potential for abuse and should be categorized as a schedule IV drug.

By scheduling carisoprodol, the Board hopes to accomplish three goals.

1) Reduce misuse and abuse of this drug. Data from several sources have shown that carisoprodol is increasingly being abused by patients who “doctor shop”, provide false symptoms, and forge prescriptions.

2) Increase patient safety. A decline in carisoprodol use would reduce the medical risk for overdose when combined with alcohol and other drugs, and would reduce carisoprodol dependency and addiction among the citizens of Washington State.

3) Increase provider awareness of the potential problems associated with this drug in the medical community so that prescribers are more cautious in the use of carisoprodol.

Section 2. General goals and specific objectives of the proposed rule’s authorizing statute

The general goal of RCW 69.50.201 is for the Board to add a substance to the drug schedule if it possesses the potential for abuse.

The board is directed to examine the following eight factors when considering scheduling a drug:

1) Does the drug pose an actual or relative potential for abuse?
2) Is there scientific evidence about the drug's pharmacological effect?
3) What is the current scientific knowledge regarding the substance?
4) What is the history and current pattern of abuse?
5) What is the scope, duration, and significance of abuse?
6) What is the risk to public health?
7) What is the potential of the substance to produce psychic or physiological dependence or liability?
8) Is the substance an immediate precursor of a controlled substance?

After assessing the eight factors above, the Board makes a determination whether or not a substance should be scheduled, and if so, what schedule or rating the substance should have. The Board can place a substance in "controlled status" by designating it as Schedule I through IV. Schedule I substances have the highest level of actual or potential for abuse including but not limited to potential for addiction. Schedule I drugs are illegal in the U.S. Drugs assigned to Schedule II or Schedule III usually show abuse potential during their drug development and the Food and Drug Administration (FDA) assigns the schedule before approval. A drug is categorized as a Schedule IV controlled substance when clinical usage demonstrates the drug has actual or relative potential for misuse and abuse, but less than lower number scheduled substances. The Board is further guided on what schedule a substance should be designated based upon schedule criteria in chapter 69.50 RCW and chapter 246-887 WAC.

RCW 69.50.201 directs the Board to place a substance in Schedule IV if it finds that that the substance:

1) Has a potential for abuse.

2) Has a currently accepted medical use in treatment in the United States.

3) If abused, may lead to physical dependence or psychological dependence relative to (less than) Schedule III substances.

Section 3. Proposed rule justification

After receiving the petition, the Board directed staff to start an investigation on whether carisoprodol should be scheduled. They completed a thorough assessment of the drug literature and experience with carisoprodol. Staff found information on the eight criteria identified in RCW. The staff also collected carisoprodol information from other states, and obtained information from surveys of both pharmacists and physicians. The

Department of Health's staff found that carisoprodol meets the criteria for warranting being scheduled. See Appendix C for the complete assessment of carisoprodol.

In addition to these efforts, the Board has held several stakeholder meetings since 2006. During these meetings, the Board met with stakeholders, staff, and other interested parties in an open meeting format to discuss the implications of scheduling carisoprodol.

Section 4. Individual rule cost/benefit analysis

The proposed rule would revise WAC 246-887-170 to add carisoprodol to the existing list of scheduled substances. There are currently 48 substances on the Schedule IV list. If adopted, carisoprodol would be the 49th legend drug listed in WAC 246-887-170 Schedule IV controlled substances.

The University of Washington School of Pharmacy survey determined the impact of changes in carisoprodol (Soma) scheduling on prescribers, wholesalers, healthcare entities, and hospitals. The Department mailed 1,060 surveys and received 307 responses for a response rate of 29%.

The table below summarizes how scheduling carisoprodol as a Schedule IV substance will impact affected parties.

Table 1

Responsible Party	Require Activity/Frequency	Cost
Prescribers: Physicians. Osteopaths, Advanced Registered Nurse Practitioners, Dentists, Podiatrists, Naturopaths, Pharmacists, Osteopathic Physicians, and Osteopathic Physician Assistants	Add DEA number to prescription. Change in approach in prescribing carisoprodol	Very little impact. Only a very few prescribers that do not have one will need to obtain a DEA number at $551 for three years. It will be more difficult for patients to obtain carisoprodol prescriptions. They will have to see the prescriber more often or see a pain specialist.
Prescribers: See above		Expect them to be more cautious in prescribing with increased awareness and concern about potential carisoprodol abuse.

Responsible Party	Require Activity/Frequency	Cost
Pharmacist, Dispensing	Add carisoprodol to Schedule IV reports/daily, monthly	Ordering process- No impact. Pharmacists use the same form when ordering legend and scheduled drugs and print daily reports. Filling prescription process- No impact. When prescribing a scheduled drug, pharmacists must confirm that the prescriber has a registered Federal DEA number. Pharmacists currently enter prescriptions into computer and this information is automatically shown. Pharmacists only have to confirm that the prescriber has a DEA number. Filing prescriptions process- No impact. Pharmacists must file each prescription after they fill the order. Scheduling carisoprodol will require pharmacist to place the prescription in the schedule IV file, versus the legend drug file. This is the usual procedure. Biennial controlled substances report- Pharmacists have to complete a report every two years for all controlled substances. Adding carisoprodol data in this report will be a minor impact.
Manufacturers	Lost sales due to scheduling	Loss of sales description- A survey of prescribers found that only 9% would change their prescribing patterns if carisoprodol is scheduled.

Cost summary

The table above shows that scheduling carisoprodol will have a minor impact on prescribers and individual patients, but could affect manufacturers' sales.

Benefit of Scheduling Carisoprodol

Once scheduled in Washington State, carisoprodol would come under visible control of the Board with the support of the DEA. The Department of Health will also notify the

health professions of the change. This will raise prescriber awareness. There will be three independent, yet related, benefits.

1) A reduction in misuse and abuse of carisoprodol with less carisoprodol prescribed, less long-term usage, and fewer instances of the combination of carisoprodol with other drugs and alcohol;

2) Increased patient safety by a reduction in morbidity and mortality associated with carisoprodol; and

3) Increased prescriber awareness of potential abuse issues associated with carisoprodol.

1) Reduction in misuse and abuse of carisoprodol

Department of Health staff extensively examined drug literature and found the following four factors as indicators of drug misuse and abuse.

- Drug is taken in larger amount than prescribed, or for reasons other than prescribed use.
- Drug is taken in combination with other drugs and alcohol
- Drug is taken for a longer period of time than intended or prescribed
- Drug is obtained under false pretenses (e.g., "doctor shopping" to obtain multiple prescriptions, illegal black market "street sales", and use of forged prescriptions)

The following studies demonstrate carisoprodol is being misused and abused.

Bramness et. al. (7) conducted a broad-based study of carisoprodol in Norway. They examined carisoprodol use by 53,889 woman and 29,824 men. They concluded that carisoprodol prescriptions were skewed with as many as 32% of the patients receiving more than 15 defined daily doses and more than 15% receiving more than 75 doses in 2004. These users also received more benzodiazepines and opioids. They found that the patients used three or more doctors for prescriptions, commonly known as "doctor shopping." They concluded that the high level of use and abuse of carisoprodol should be a concern.

Reeves et. al. (19) surveyed 40 patients that had been taking carisoprodol for three months or more. Twenty patients had no history of substance abuse. One of these patients indicated that they attempted to obtain extra prescriptions. Of the 20 patients with a history of abuse, four indicated that they attempted to get extra prescriptions. Reeves found that some patients used carisoprodol to augment the effect of another drug, especially those individuals with a history of substance abuse.

Bailey et. al. (20) examined results of comprehensive drug screenings from the University of California, San Diego Medical Center ordered for purposes of patient care. From January 2001 to July 2001, there were 4,245 comprehensive drug screens performed. Bailey examined results from urine specimens from 19 patients were carisoprodol was found. In seven cases, clinical history suggested that carisoprodol was used primarily for medical purposes. He found that in seven other cases the patients abused the drug or used the drug in a suicide attempt or gesture. In the last group of five patients, the reason for use could not be determined. He concluded that carisoprodol has become an unrecognized drug of abuse and suggests that it be included in comprehensive drug screenings.

Mathias Forrester (5) examined data from six poison centers in Texas from 1998 to 2003 to describe abuse of carisoprodol He found that carisoprodol abuse as measured in the percentage and real numbers of calls received that are classified as abuse calls is increasing in Texas. From 1998 to 2003, the number of abuse calls associated with carisoprodol has increased from 83 in 1998 to 235 in 2003.

Boothby et. al. (21) conducted an extensive review of literature on the efficacy and abuse potential of carisoprodol. She reviewed results from nine clinical trials and concluded that the "literature review produced little evidence to support the use of carisoprodol in pain control." Her research also showed that patients with a history of previous substance abuse are more likely to abuse carisoprodol. She concluded that "at the very least, states should reschedule carisoprodol as a schedule IV controlled substance to minimize chronic misuse and abuse."

Owens et. al. (9) reviewed Idaho Medicaid Pharmacy and Medical Claims Data from 2005. He compared drug use for 340 patients that used carisoprodol to drug use for 453 patients that used other types of skeletal muscle relaxers (SMRs). He concluded that the carisoprodol users, as compared to patients that used other SMRs, were more likely to use the drug in combination with opioids (chemicals that create morphine-like reactions). The carisoprodol users had a past diagnosis indicating other drug dependence or abuse; 34.1% compared to 21.4% for other SMR users. The study also determined that 80% of the long term users of carisoprodol were willing to pay for drugs out of pocket after third party coverage was discontinued. None of these respondents indicated that they tried other SMRs. Taken collectively, Owens concludes that patients that using carisoprodol for long periods of time displayed abuse potential more frequently than long-term users of other agents.

In 2006, the Florida Department of Law Enforcement published "Drugs Identified in Deceased Persons by Florida Medical Examiners." The examiners found benzodiazepines, carisoprodol, and opioids more often than illicit drugs. These drugs were found in both lethal (73%) and non-lethal (63%) levels during the year (22).

Carisoprodol is a drug that is abused by patients who exceed the recommended doses and duration of drug use, and who present false symptoms and information to obtain larger quantities of the drug. Some of these patients sell their extra prescriptions illegally on the

street. This term is generally referred to as "diversion." University of Washington Professor Michaelene Kedzierski, a recognized drug abuse expert, states that "it is widely known in the Seattle area drug-using community that one can request a prescription, obtain a supply (of carisoprodol), and sell it on the street" (23). The street value of carisoprodol ranges from $1 to $5 per tablet. In addition to impaired users, this activity presents a risk to public health and safety due to crime associated with illegal drug sales.

2) Increased patient safety (reduction in morbidity and mortality associated with carisoprodol)

An increasing trend of carisoprodol abuse has been documented in evidence collected in Snohomish, King, and Pierce Counties. Dr. Caleb Banta-Green of the Alcohol and Drug Abuse Institute at the University of Washington analyzed data from the 22 Emergency Departments (EDs) that participate in the DAWN system and data from other morbidity and mortality reports in the Seattle-Bellevue-Tacoma area (24). His results show that carisoprodol can be dangerous and associated with death. Its potent sedating effects are routinely added to other drugs of abuse, and carisoprodol has often been overlooked in drug abuse determinations.

DAWN made national estimates of drug-related visits to hospital emergency departments based on data from the hospitals that participate in the network. DAWN relies on a national sample of general, non-federal, hospitals that operate 24-hour emergency departments. They sample nationally with an oversampling of hospitals in selected metropolitan areas. For the years 1994, 2001, 2004, 2005 and 2006, DAWN estimates the number of emergency room visits involving carisoprodol has increased from 6,569, 11,239, 17,366, 19,512 and 24,506, respectively.

The Washington State Department of Health tracks data associated with patient cases that result in mortality. Table 2 shows drug overdose cases since 2003 in which carisoprodol has been found in mortality cases, often in combination with other drugs (25).

Table 2

Washington State Mortality Cases with Carisoprodol Detected with

Opiates, Illegal Drugs, and Other Drugs, 2003-2007

		Prescription Opiate Reported		Illegal Drug Reported		Mean Number of Drugs Reported
Year	Total	Number	Percent	Number	Percent	
2003	5	3	60.0	1	20.0	5.4
2004	10	7	70.0	2	20.0	5.0
2005	15	11	73.3	3	20.0	3.5
2006	17	9	52.9	4	23.5	5.0
2007	13	8	61.5	1	7.7	4.1

Sources:
Includes residence and/or occurrence in Washington State.
Cases selected if any cause-of-death text contained “CARISO”.
Cases selected if manner of death accident.
Illegal drugs include heroin, cocaine, and methamphetamine (no reports of LSD, PC, MDMA).
More cases could have had an illegal drug, but the information on the death certificate was too vague to determine. Many reported “opiate” without specifying the type or reported “morphine” without specifying if it was pharmaceutical morphine or not.

Center for Health Statistics, Washington State Department of Health, July 9, 2009

The safety of carisoprodol is a concern in the European countries as well. Hoiseth and his Norwegian colleagues investigated, at the Norwegian Institute of Public Health, all forensic autopsies from 1992 to 2003 and detected carisoprodol (26). They found that carisoprodol can be fatal in concentrations below those indicated in previous studies. The increased number of cases with carisoprodol correlated to increased sales figures for the drug. Norway withdrew the drug from its market in May 2008.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (Agency) reviewed the Norwegian, and other, studies and found evidence for an increased risk of abuse or addiction as well as psychomotor impairment. The Agency subsequently recommended the suspension of the marketing authorizations of all carisoprodol-containing medicinal products in the other eleven European Union countries (27).

3) Increased prescriber awareness of potential abuse issues associated with carisoprodol.

Reeves surveyed 100 physicians with a brief questionnaire about commonly prescribed medications, including carisoprodol and meprobamate. They were to select from the lists of medications substances that were controlled substances or are metabolized to controlled substances. The results were that 95% of the prescribers were aware that

meprobamate was a controlled substance and has abuse potential. Only 39% were aware that carisoprodol metabolizes to meprobamate and that carisoprodol has abuse potential (17).

Reeves, et. al., also evaluated the abuse potential of carisoprodol by assessing duration of its use. Because carisoprodol is approved for the treatment of acute muscular pain, the average length of time of usage for the patients in his study was 4.8 months. Reeves concluded that physicians prescribe carisoprodol should be cognizant of the duration of the therapy, especially for patients who have a history of substance abuse.

The controlled substances system requires the manufacturer to educate health care providers about the scheduled substances they produce. This education campaign consists of mailings to the practitioners and continuing educating programs. Once prescribers gain an awareness of the potential abuse issues associated with carisoprodol, the Board anticipates that prescribers will be more careful when prescribing carisoprodol to individuals that have problems with abuse or addiction. This will reduce the events of unintentional substance abuse due to tolerance, addiction, and toxicity of the substance.

By scheduling carisoprodol, physicians will be aware of the potential abuse issues of patients that have a history of dependency and abuse. The Board assumes that this will decrease exposure of this abused drug to patients that have a history of dependency and abuse.

Benefits Summary and Conclusion

By scheduling carisoprodol, physicians will become more aware of the potential abuse issues of patients that attempt to use excessive amounts of carisoprodol or use carisoprodol in combination with other drugs and alcohol. Given experience with other drugs that become scheduled, frequency of abuse of carisoprodol will decrease, which will indirectly reduce the number of emergency room visits and mortality cases where carisoprodol is present.

Collectively, the probable benefits of scheduling carisoprodol outweigh the probable costs.

Section 5. Description of alternatives considered and least burdensome determination

An alternative approach would be to get drug purchasing groups to remove carisoprodol from their formularies. The health care plans could gain from reducing higher health care costs of drug abuse. Prescribers would be required to make a special effort to prescribe carisoprodol and the drug would have a higher co-pay for the patient.

There are more than 50 pharmacy benefits companies that determine formularies for Washington State citizens. Many of them are out-of-state. There is no established link to the Board and the usage data would be challenging to obtain. The Board does not have

authority to require pharmacy benefits managers to comply. Another obstacle is that the majority of carisoprodol prescribed is in the form of an inexpensive generic drug. Some purchasing groups may choose the lower cost generic carisoprodol.

While there would be few costs for the health plan, the time spent by the prescribers and the pharmacies in resolving the patient's needs and insurance requirements could be significant. The health plans would not want to be seen as "drug police." Most likely some plans might restrict carisoprodol, while others may not. In contrast to changes in scheduling, pharmacists consider changes in health plan requirements as burdensome. The important communication that carisoprodol is a drug of abuse may not occur.

Section 6. Determine that the rule does not require those to whom it applies to take an action that violates requirements of another federal or state law.

The proposed rules for scheduling carisoprodol by state or federal government requires a specific set of information. The actual schedules are the same. What can vary is that due to their unique circumstances, a state may schedule a drug that has not been scheduled at the federal level. Carisoprodol is an example of one of these drugs; since 13 states have scheduled the drug and the federal government has not.

Given that federal and state regulatory agencies use the same schedules, there does not appear to be any potential to require those to whom the rule applies to take an action that violates requirements of another federal or state law. The more stringent rule must be observed whether it is a federal or state requirement.

Section 7. Determine that the rule does not impose more stringent performance requirements on private entities than on public entities unless the difference is required in federal or state law.

The rule does not impose more stringent performance requirements on private entities than on public entities.

Section 8. Determine if the rule differs from any federal regulation or statute applicable to the same activity or subject matter and, if so, determine that the difference is justified by an explicit state statute or by substantial evidence that the difference is necessary.

The DEA continues to categorize carisoprodol as a Drug of Concern. A September 2007 DEA Bulletin (28) noted that diversion and abuse of carisoprodol has increased and cited statistics from three national data bases to support their determination.

Although the FDA has not scheduled carisoprodol, it has required the company to include in their labeling for the new carisoprodol dosage that carisoprodol may cause dependence, withdrawal, and abuse (29).

Section 9. Demonstrate that the rule has been coordinated, to the maximum extent practicable, with other federal, state, and local laws applicable to the same activity or subject matter.

There are no other applicable laws.

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29. Soma® (carisoprodol) Tablets for Oral Use. Package Insert Rev. 9/07

SOMA (6_6_2009) AM, PB, TF

Appendix A

National Estimate of Number of Drug Cases where Carisoprodol was Detected

	2000	2001	2002	2003	2004	2005	2006	2007
Carisoprodol								
Number	480	1890	2,946	3,297	2,757	3020	3558	4420
Percentage	0.09%	0.10%	0.16%	0.19%	0.16%	0.17%	0.18%	0.24%

Sources:
National and Regional Estimates for the 25 Most Frequently Identified Drugs, National Forensic Laboratory Information System, Year 2007, Annual Report, Drug Enforcement Administration
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Appendix B.

UW Law student petition to schedule Carisoprodol

Board of Pharmacy
Washington State Department of Health
1300 SE Quince Street, P.O. Box 47860
Olympia, Washington, 98504-7860

December 9, 2002

Dear Board Members:

As part of a project for our law class at the University of Washington School of Pharmacy, we would like to petition the Board of Pharmacy to classify carisoprodol (Soma®) as a schedule IV controlled substance. The National Board of Pharmacy (NABP) believes that carisoprodol should be classified as a schedule IV substance. In addition, sixteen state boards of pharmacy currently consider carisoprodol to be a controlled substance.[1]

In accordance with the criteria listed in RCW 69.50.201, we would like the Board to consider the following:[2]

(i) **the actual or relative potential for abuse**;

Carisoprodol has been documented for abuse on its own, but is more frequently reported in conjunction with other substances including alcohol, acetaminophen with codeine, benzodiazepines, and other narcotics and illegal drugs, such as cocaine.[3] In a small, forty subject study, (20 subjects with a history of substance abuse and 20 subjects with no history of abuse) patients who had been taking carisoprodol for over three months were given a questionnaire. The results indicated that patients with a history of substance abuse were more likely to use carisoprodol in larger amounts than prescribed (40%) and for an effect other than for which it was intended (30%). These results were statistically significant when compared to subjects without a history of abuse (20% reported over use and 10% used it for another effect).[4]

(ii) **the scientific evidence of its pharmacological effect, if known**;

Carisoprodol is a central nervous system depressant with both sedative and skeletal muscle relaxant properties. The exact mechanism of action is unknown, but it is thought to result from sedation rather than directly stimulating the skeletal muscle causing relaxation. There are very few studies demonstrating the efficacy of oral skeletal muscle relaxants (SMRs), and many

[1] National Association of Boards of Pharmacy (NABP): Scheduling of carisoprodol to schedule IV; Resolution 98-6-02: Phoenix AZ
[2] Revised Code of Washington 69.50.201, Uniform Controlled Substances Act Article II Enforcement of chapter-Authority to change schedule of controlled substances; 2002
[3] Reeves R, Liberto V. Abuse of combinations of carisoprodol and tramadol. South Med J 2001; 94: 512-514

physicians are skeptical about their widespread use for many reasons. First of all, there is a lack of evidence demonstrating that carisoprodol is clinically significant as a skeletal muscle relaxant. Secondly, muscle spasms are a physiological response that is normal and protective, and interruption of this response may lead to further injury. In addition, there are many different types of muscle spasms, and it is indicative that SMRs are not effective for all types of spasms.[5]

(iii) **the state of current scientific knowledge regarding the substance;**

Many case reports have shown the potential for abuse of carisoprodol. A cat breeder was able to obtain carisoprodol via a veterinary mail-order catalog. This patient developed a tolerance to increasing doses in addition to a daytime abstinence syndrome that was relieved by subsequent doses of carisoprodol. She was admitted to the hospital after an overdose of carisoprodol and experienced withdrawal symptoms including hallucinations, tremor, and disorientation for 48 hours.[6] In a letter to *Archives of Family medicine*, Ronald J Dougherty, a physician specializing in addiction medicine, explains that in 24 years in the field of chemical dependency 10% to 15% of patients referred to him were misusing carisoprodol or meprobamate. He elaborates on a treated patient that was a long time carisoprodol abuser who never abused alcohol or any drug in the past. In spite of several attempts at detoxification rehabilitation she continued to alter and obtain prescriptions for carisoprodol. As a result of long time use and abuse, the patient was diagnosed with end stage liver disease, bone marrow depression, total pancytopenia and anemia.[7]

There is also increased concern of carisoprodol use in combination with other legal and illegal drugs to enhance their effects. One study showed that tramadol and carisoprodol were used concurrently for psychotropic effects.[3] In addition, a physician describes how several of his patients used carisoprodol in an attempt to extend the action of some drugs and especially to come down more slowly from other drugs, particularly cocaine.[8]

(iv) **the history and current pattern of abuse;**

Carisoprodol was introduced in the 1950s and was widely used in both human and veterinary medicine. At the time of FDA approval it was not reported to have any dependence-producing properties or any indication of abuse.[4] The widespread use of carisoprodol was due

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[4] Reeves R, et al. Carisoprodol (Soma): Abuse potential and physician unawareness. J Add Disease; 18(2): 51-57
[5] Littrell R, Hayes L, Stillner V. Carisoprodol (Soma): A new and cautious Perspective of an old agent. South Med J 1993; 86: 753-756
[6] Rust GS, Hatch R, Gums JG. Carisoprodol as a drug of abuse. Arch Fam Med. 1993 Apr;2(4):429-32
[7] Dougherty RJ. Carisoprodol should be a controlled substance. Arch Fam Med. 1995 Jul;4(7):582
[8] Chop,W. Should carisoprodol be a controlled substance? Arch Fam Med 1993 Sep;2:911

partly to its availability without a prescription through veterinary mail-order catalogs. By the year 1978 the drug was recognized as having abuse potential. Carisoprodol abuse has amplified because of the lack of availability of preferred drugs due to their status as controlled substances. To illustrate, a physician is more likely to prescribe a legend drug than a controlled substance if it is an appropriate course of therapy. Carisoprodol is an easy target for those with substance abuse problems due to its increased accessibility throughout the United States. One of the greatest concerns however, is that many physicians are unaware of the abuse potential of carisoprodol and of its metabolism to meprobamate, a schedule IV drug.[4]

(v) **the scope, duration, and significance of abuse**;

In 1978, the first published case of carisoprodol dependence emerged.[9] Since then, according to the DEA, it has become the most widely abused non-scheduled prescription drug in the United States. The Drug Abuse Warning Network (DAWN) collects data on substances abused for dependence, suicide, or psychic effects encountered at 458 emergency departments (ED) nationwide. In 2001, carisoprodol was reported as the substance of abuse in 2,944 ED episodes (29th ranked drug causing a ED episode), slightly less than lorazepam (3,593 ED episodes, 25th), but more than diazepam (2,379 ED episodes, 33rd). Of the 2,944 ED episodes, 2,066 were reported as female users with the majority of abusers reported as Caucasian between the ages of 35-44 years of age.[10] It is obvious that the non-medical use of carisoprodol is an increasing problem. In an abuse situation, intake of the drug escalates beyond the amount indicated for medical treatment. Larger doses are used to obtain sedative effects and to avoid withdrawal symptoms possibly associated with the metabolite meprobamate.[9,11] Carisoprodol is more commonly used in combination with other drugs for purposes such as prolonging the effect of alcohol or a narcotic, to achieve the same effect with a smaller amount of alcohol or a narcotic, or to increase the effect of the primary drug of abuse.[12] Carisoprodol has been reported in combination with drugs such as ethanol, diazepam, alprazolam, hydrocodone,[13] and tramadol.[3] One study, analyzing the toxicology results of 24 carisoprodol related deaths in Jefferson County, Alabama, had carisoprodol in combination with various co-intoxicants in all 24 cases.[13] It is apparent that with increased abuse of carisoprodol there is an increased risk of harm to the

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[9] Morse R, Chua L. Carisoprodol dependence: A case report. Am J Drug Alcohol Abuse 1978; 5(4):527-30
[10] Data compiled from the Drug Abuse Warning Network (DAWN) by the Substance Abuse and Mental Health Services Administration, US Dept. of Health and Human Services, Rockville, Md. (http://www.dawninfo.net)
[11] Luehr JG, Meyerle KA, Larson EW. Mail-order (veterinary) drug dependence. JAMA 1990; 263: 657
[12] Elder N. Abuse of skeletal muscle relaxants. Am Family Physician 1991; 44: 1223-26

user. Of the 2,944 ED episodes reported for carisoprodol in 2001, 2,216 ED episodes were due to overdose, most likely in combination with other drugs.[10] In addition, there has been evidence of illicit commercial activity surrounding carisoprodol. A man found having a seizure in his car was admitted into the University of California, San Diego Medical Center and was found in possession of 150 homemade tablets. Later analysis showed that carisoprodol was the sole drug in this homemade formulation.[14]

(vi) **the risk to the public health;**

The LAPD Drug Recognition Expert Unit states that the Drug Enforcement Administration is continuously reviewing carisoprodol. Information has been received from medical professionals, state regulatory authorities, and law enforcement personnel indicating that the drug is being diverted, trafficked and abused. Federal, state, and local sources of information indicate that carisoprodol abuse is significant, widespread and increasing. Analysis of data obtained for the period 1980-1996 from the System to Retrieve Information from Drug Evidence (STRIDE) revealed law enforcement personnel in twenty-seven states and the District of Columbia have encountered carisoprodol. There are over 229 cases in STRIDE that involve seizures, undercover purchases or "gifts" of carisoprodol.[15]

Reports of carisoprodol abuse include patients trying to obtain prescriptions from multiple physicians, forging prescriptions, and patients that regularly obtain carisoprodol through veterinary mail order services.[12] One risk to public health includes theft. Patients wanting carisoprodol for their own personal use will find ways to obtain the actual drug or to obtain money to buy the drug. Chronic abuse may lead people to steal prescription pads from doctor's offices, steal money from others, or break into pharmacies to obtain carisoprodol. These risks put others in danger of being victimized. Doctors, pharmacies, and the public are at risk of being robbed or cheated in order for abusers to obtain carisoprodol. Doctors are at risk of being "fooled" into writing prescriptions for individuals who do not need carisoprodol.[3] Another risk to public health is many patients and abusers taking the medication may drive or take care of children while under the influence.

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[13] Davis GG, Alexander CB. A review of carisoprodol deaths in Jefferson County, Alabama. South Med J 1998; 91: 726-30

[14] Bailey DN, Briggs JR. Carisoprodol an unrecognized drug of abuse. Am J Clin Pathology 2002; 117(3): 396-400

[15] Data complied from Los Angeles Police Department Drug Recognition Expert Unit; 1997 (http://www.ci.la.ca.us/LAPD/traffic/dre/soma.htm)

(vii) **the potential of the substance to produce psychic or physiological dependence liability**;

The National Association of Boards of Pharmacy has reported carisoprodol as the most abused non-controlled legend drug[1]. Despite this knowledge of abuse, limited evidence exists regarding the ability of carisoprodol to produce psychic or physiological dependencies. Meprobamate, a schedule IV controlled substance, is the major metabolite of carisoprodol.[16] Several case studies have been reported in which patients developed meprobamate dependence secondary to use of carisoprodol.[5] Two case reports described patients who had signs of true withdrawal syndrome, while another report involved a fatality linked to carisoprodol abuse.[6] One prospective withdrawal study conducted on prisoners examined the effects of withdrawing carisoprodol on nine inmates who had been on varying doses (700 to 2100mg) for at least nine months.[17] During the withdrawal period the patients were monitored for abstinence symptoms. The symptoms reported during the withdrawal period, included anxiety, insomnia, irritability, and muscular pain. Overall, the evidence of carisoprodol causing physiological dependence is both limited and poor. Despite these limitations, it appears that some individuals may experience withdrawal symptoms associated with physiological dependence.

The Drug Abuse Warning Network reported carisoprodol as being in the top forty drugs associated with emergency department episodes.[18] Twenty nine hundred forty-four emergency room episodes involving carisoprodol were reported in the year 2001. The motives for drug use include, from greatest to least, psychic effects, suicide, and other unknown motives. However, no patients had reported using for dependence purposes. This report, then, provides data that indicates carisoprodol is being used for psychic effects.

(viii) **and whether the substance is an immediate precursor of a controlled substance**.

Carisoprodol undergoes hepatic biotransformation to three primary metabolites: hydroxycarisoprodol, hydroxymeprobamate, and meprobamate.[5] Meprobamate, introduced in 1955, is a schedule IV drug prescribed to treat anxiety, tension and associated muscle spasms. Patients taking excessive amounts of meprobamate can experience psychological and physical dependence. This consequence of meprobamate use may contribute to carisoprodol abuse.

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[16] MICROMEDEX® Healthcare Series: MICROMEDEX, Greenwood Village, Colorado (Edition expires (2001))
[17] Wyller TB, Korsmo G, Gadeholt G. Dependence on carisoprodol (Soma): A prospective withdrawal study among prisoners. Tidsskr Nor Laegeforen 1991 Jan 20;111(2):193-5
[18] Drug Abuse Warning Network. DAWN Detailed ED Tables; Table 4.17. Top 40 single-drug and multiple-drug ED episodes by drug use motive, 2001

We thank you for your consideration. We believe that classifying carisoprodol as a schedule IV drug will decrease diversion, increase physician awareness regarding the potential for abuse and encourage special caution in patients with a history of drug abuse, and decrease the street use of this drug.

Sincerely,

Harrison Aihara Emily Cooper Wendy Exely Jessica Hilton

Helen Marshall Hollye Powell David Strider

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Appendix C.

Stakeholder Meeting

Scheduling of Carisoprodol:

Feb 7, 2008; revised May 19, 2008

Briefly describe the proposed rule.

The Board of Pharmacy was petitioned by students from the University of Washington School of Pharmacy law class to classify carisoprodol (SOMA)™ as a schedule IV substance due to its abuse alone and in combination with other abused drugs.

Goal: Determine if the benefits of scheduling carisoprodol as a Schedule IV substance of the Uniformed Controlled Substances Act outweigh the costs of scheduling.

The drug substance carisoprodol was developed and introduced to the market as SOMA™ (carisoprodol) and SOMA™ COMPOUND (carisoprodol and aspirin) by Carter-Wallace Inc., now MedPointe Pharmaceuticals in 1959. Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of acute, painful musculoskeletal conditions. Carisoprodol belongs to a group of drugs known as skeletal muscle relaxants. Carisoprodol has not been successful in competing with other skeletal muscle relaxants for inclusion in drug formularies. The Washington State Pharmacy and Therapeutics Committee stopped covering carisoprodol in 2004 due to concerns about abuse and addiction and the availability of other medications with similar efficacy.[1]

The Board of Pharmacy has the authority to designate a medication as a controlled substance under the Uniform Controlled Substances Act. Chapter 69.50.201 RCW Enforcement of Chapter-Authority to change schedules of controlled substances provides the Board the authority to change schedules of controlled substances. The Board of Pharmacy may add substances to or delete or reschedule controlled substances.

In making a determination regarding a substance, the Board shall consider the following questions **(i)-(viii)** in RCW 69.50.201. The responses to these questions represent both views, those that support carisoprodol scheduling and those that oppose carisoprodol scheduling. The responses to the questions demonstrate the benefits of scheduling carisoprodol compared to the costs of scheduling. The decision to schedule a substance is based on the scientific merit.

In making the determination regarding a substance, the board shall consider the following:

(i) the actual or relative potential for abuse

The abuse of carisoprodol is described in multiple case reports[2-8], often in conjunction with other substances including alcohol, benzodiazepines, and opiates.[9] Data from drug abuse tracking systems including the Idaho Medicaid data[10], [the] Drug Abuse Warning Network (DAWN) 2004[11] and 2005 results, [12] and the

National Forensic Laboratory Information System (NFLIS) 2004[13] and 2006[14] reports confirm the consistent abuse and misuse of carisoprodol. For example, the DAWN report collects emergency department (ED) drug-related visits, including 22 hospitals in the Seattle-Bellevue-Tacoma area. In the DAWN 2004 report 6% of the pharmaceutical misuse/abuse ED visits were attributed to muscle relaxants. The most frequent muscle relaxant was carisoprodol, which was involved in 17,366 or 4% of ED visits in 2004. The number of ED misuse/abuse visits in the DAWN 2005 report attributed to carisoprodol increased to 19,665 visits. The 2001 DAWN report cited by the UW pharmacy students in their petition to the Board of Pharmacy identified 2,379 ED episodes. Note: DAWN methodology changed with the 2003 report.

The Washington State Pharmacy Association (WSPA) conducted a pharmacist survey in May 2007. The respondents overwhelmingly support scheduling carisoprodol. Pharmacists have seen an increasing use and abuse of carisoprodol in Washington State. Physicians have had to use patient contracts to prevent early refills and over use of carisoprodol. The pharmacists want a prescription monitoring program in Washington State to help providers identify and address drug seeking behavior which is an increasing problem. The WSPA Board of Directors has endorsed the re-scheduling of carisoprodol by the Washington State Board of Pharmacy.[15]

Michaelene Kedzierski, a Washington State pharmacist, is recognized for her experience and knowledge in substance abuse/addiction. She wrote a letter to the Board supporting the rescheduling of carisoprodol to decrease the risk to public health and safety.[16] Professor Kedzierski describes the use and misuse of carisoprodol she has observed both in the care of patients and the street sales. Patients request carisoprodol for mood-altering effects when other drugs are not available. They can obtain carisoprodol as many providers are not aware of its widespread use and misuse and its metabolism to meprobamate, a schedule IV controlled substance.

On the other hand, carisoprodol has been a legend drug for nearly 50 years. Practitioners have found it to be a useful drug acutely for painful musculoskeletal conditions. The manufacturer states that carisoprodol was considered for scheduling as a controlled substance by the federal Food and Drug Administration in 1997.[17]

The DEA requested a scientific and medical evaluation by the FDA. The FDA invited manufacturers and other interested persons to appear and to submit comments and convened its Drug Abuse Advisory Committee to review the issues.

The issue for the FDA was whether there was adequate scientific data to schedule carisoprodol-containing drugs. The DEA made extensive presentations about the

misuse abuse of carisoprodol. The FDA Committee, however, determined that additional data developed by using current scientific methodology would be required to schedule carisoprodol-containing medications. The drug had been on the market more than 35 years at that time.

The proponents of carisoprodol, as a basis for determining a lack of dependence liability and abuse, provide a dosing study of 5 patients from 1961.[18] It is described as a study of long-term administration of carisoprodol. All patients, but one, took carisoprodol for 18 days and stopped the drug without difficulties. They had no withdrawal symptoms. Carisoprodol is indicated for use in acute pain not chronic pain and an open study of 5 patients provides very little information about the drug.

(ii) the scientific evidence of its pharmacological effect, if known.

Most references state that the pharmacological effect is unknown and its metabolite, meprobamate could account for extended sedation ($T_{1/2}$=8-16h).[19] The manufacturer states that neuropharmacologic studies in laboratory animals in determining carisoprodol acts by blocking polysynaptic transmission in the descending reticular system of the brain.[20]

(iii) the state of current scientific knowledge regarding the substance

There is a lack of evidence to demonstrate that carisoprodol is a clinically significant skeletal muscle relaxant. Carisoprodol is not approved by many drug formularies as a muscle relaxant because there are safer and more effective therapeutic alternatives. An extensive literature review by the Oregon Evidence-Based Practice Center concluded: "Not one randomized trial of muscle relaxants was rated as good quality; there is little evidence of rigorous adverse event assessment; and there is (only)fair evidence that carisoprodol is effective." [21]

Programs like DAWN that are designed to collect drug abuse data are finding more and more incidences where carisoprodol is present. In the past carisoprodol was often not identified as a drug of misuse/abuse because it wasn't looked for as a drug of abuse. There is concern that many medical providers are not aware of carisoprodol abuse. That is changing. The recently implemented Ohio State prescription monitoring program chose to add carisoprodol to the controlled substances that will be tracked.[22]

The brand name drug manufacturer states that scientific and medical evidence do not satisfy the criteria to support the placement of carisoprodol in Schedule IV. The 1997 FDA review of a DEA request for scheduling of carisoprodol, is cited as proof.

(iv) the history and current pattern of abuse <u>and</u>

(v) the scope, duration, and significance of abuse

According to the System to Retrieve Information from Drug Evidence (STRIDE), a federal database for the seized drugs samples analyzed by DEA forensic laboratories, there were 60, 57, 58 and 54 carisoprodol cases involving seizure of 101, 117, 99 and 79 drug records in 2003, 2004, 2005 and 2006, respectively.[13] Since 1997 the Drug Enforcement Administration has systematically collected drug analysis results and associated information from the nations' forensic laboratories for the National Forensic Laboratory Information System (NFLIS) Report. Carisoprodol has been consistently listed in the top 25 most frequent drugs identified by the state and local forensic laboratories. In the first six months of 2006, a total of 1,565 analyzed drug items were identified as carisoprodol by the NFLIS.

The Toxic Exposure Surveillance System (TESS) reported an increase of 25% in carisoprodol exposures from 6,656 in 2000 to 8,337 in 2005. Reports by Florida Medical Examiners indicate that carisoprodol/meprobamate related deaths in Florida increased by 51% from 208 in 2003 to 314 in 2005 and surpassed opioids such as heroin, fentanyl, hydromorphone, and tramadol. The drugs for which data was collected for their report included benzodiazepines, cannabinoids, carisoprodol/meprobamate, cocaine, ethyl alcohol, GHB, Inhalants (Freon, nitrous oxide, etc), ketamine, methylated amphetamines, opioids (including tramadol), and PCP). . The poison control centers in Texas reported the top drug identification requests from law enforcement and carisoprodol was third most common medication with 1380 requests following alprazolam and APAP/hydrocodone combinations from 2002-2004.[24]

Carisoprodol has been scheduled as a controlled substance in the following 17 states: Alabama, Arizona, Arkansas, Connecticut, Florida, Georgia, Hawaii, Kentucky, Massachusetts, Minnesota, Nevada, New Mexico, Oklahoma, Oregon, Tennessee, Virginia and West Virginia. In 1997 when the FDA determined that there was inadequate evidence to support scheduling, just 6 states had scheduled carisoprodol. Since that time, 11 more states have scheduled carisoprodol.

The manufacturer claims the petition to schedule carisoprodol relies on anecdotal reports which do not represent a scientific and medical basis for scheduling. The DEA used the same kind of data in its 1997 effort to schedule carisoprodol. These reports failed to impress the FDA that scheduling was warranted.

(vi) the risk to the public health

According the 2005 DAWN report, there were 19,513 carisoprodol ER visits that involved the nonmedical use carisoprodol (roughly the same as lorazepam and ibuprofen). This was an increase from 2004, in which there were 17,366 cases involving carisoprodol. Carisoprodol was listed as the 19th of the 25 most frequently identified drugs from NFLIS in 2006 (ahead of methylphenidate, propoxyphene, lorazepam, and hydromorphone). Høiseth et al[25], published a retrospective analysis of forensic autopsy material collected from 1992-2003 in Norway. Of the 5,001 autopsies conducted during this time period, 156 had either carisoprodol and

meprobamate or meprobamate alone in their systems. Only one patient only had meprobamate and carisoprodol. All others had other chemicals.

Norway in May 2008 banned the use of carisoprodol due to safety concerns. The European Medicines Agency (EMEA), which makes recommendations to the European Union, reviewed the scientific findings from Norway and has concluded that the risks of these medicines are greater than their benefits. EMEA has recommended the suspension of marketing authorizations in those Member States where the product is approved..[26] The Agency has suspended carisoprodol marketing activities and will present their concerns to the European Union.

Current Washington State Board of Pharmacy members have shared that abuse of carisoprodol has been an issue in several pharmacist discipline cases.

The manufacturer states that scheduling carisoprodol would negatively affect patients and prescribers. The patient would be stigmatized by taking a controlled substance prescription. Many physicians prefer not to prescribe controlled substances. Therefore, some clinicians may prescribe an unscheduled drug in the place of carisoprodol.

(vii) the potential of the substance to produce psychic or physiological dependence liability

A 2003 study with 5 subjects illustrates that patients receiving long term, very high dose (>2100mg/ day) carisoprodol treatment experienced significant somatic withdrawal symptoms in 3/5 patients and minimal symptoms in the other two patients. Common symptoms included insomnia, anxiety, headache, irritability, and back pain.[27] Also, according to the 1961 study commonly cited by manufacturer "with 2,500mg of carisoprodol, evaluated in 15 tests, only one of 15 patients identified it as being "dope" (opiate), and this patient identified it as such on only two of six observations. The predominate effects subjectively and objectively were similar to those of a barbiturate or alcohol, and not similar to those of an opiate." In the portion of the experiments which evaluated the use of carisoprodol for twenty-four-hour substitution for morphine, the "… carisoprodol seemed barbiturate-like in many respects, the study was also controlled by substituting intramuscular pentobarbital in an average dose of 1.11g divided among five doses…" Numerous reports identify the barbiturate or alcohol-like effects of carisoprodol. Barbiturates, of course, are scheduled medications.

Again the manufacturers point out the 1961 study, with 5 subjects, which illustrates how patients were able to take increasing doses chronically and have the therapy abruptly discontinued, without characteristic patterns of intoxication or of abstinence signs[18]. A more recent study stated the available literature provides no data regarding the comparative risks of abuse and addiction from skeletal muscle relaxants.[21]

(viii) whether the substance is an immediate precursor of a controlled substance

The scheduled medication, meprobamate is a metabolite of carisoprodol. An immediate precursor is defined as a substance used in the manufacturer of controlled substances. Meprobamate is not used in the manufacturer of carisoprodol, but is a substance derived pharmacologically from carisoprodol

Carisoprodol is metabolized into meprobamate, a schedule IV anxiolytic agent. According to Olsen et al (1994)[19], in most subjects, carisoprodol is rapidly metabolized with a half-life between 53-145min. Within 2.5 hours meprobamate serum levels exceed those of carisoprodol. Serum concentrations of meprobamate observed in this study after a 700 mg oral dose (twice therapeutic) of carisoprodol are not far from those after intake of therapeutic doses of meprobamate.[1]

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