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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-333]

Schedules of Controlled Substances: Placement of Carisoprodol 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 carisoprodol, including its salts, isomers, and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, into Schedule IV of the Controlled Substances Act (CSA). This action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing. The decision of the Administrator is reprinted in its entirety below.

EFFECTIVE DATE: [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

ALJ Docket No. 10-46

Background

This is a proceeding under 21 U.S.C. 811(a) for the issuance of a rule placing carisoprodol in schedule IV of the Controlled Substances Act (CSA). Under this provision, "the

Attorney General may, by rule," add a "drug or other substance" to one of the five schedules of controlled substances, "if he . . . finds that such 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)] for the schedule in which such drug is to be placed." 21 U.S.C. 811(a). However, a rule made under this provision "shall be made on the record after opportunity for a hearing pursuant to the rulemaking procedures prescribed by subchapter II of chapter 5 of Title 5." Id.

"[W]ith respect to each drug . . . proposed to be controlled," the CSA requires that the Attorney General consider eight factors in making the findings required under both subsections 811(a) and 812(b). These are:

(1) [The drug's] 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 significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

21 U.S.C. 811(c).

However, "before initiating proceedings . . . to control a drug . . . and after gathering the necessary data," the Attorney General is required to "request from the Secretary a scientific and medical evaluation, and his recommendations, as to whether such drug . . . should be controlled." Id. 811(b). The statute further provides that "[i]n making such evaluation and recommendations, the Secretary shall consider the Factors listed in paragraphs (2), (3), (6), (7), and (8) of subsection (c) . . . and any scientific or medical considerations involved in paragraphs (1), (4),

and (5) of such subsection. The recommendations of the Secretary shall include recommendations with respect to the appropriate schedule, if any, under which such drug . . . should be listed." Id.

Finally, "[t]he recommendations of the Secretary to the Attorney General shall be binding as to such scientific and medical matters, and if the Secretary recommends that a drug . . . not be controlled, the Attorney General shall not control the drug . . . . If the Attorney General determines that these facts and all other relevant data constitute substantial evidence of potential for abuse such as to warrant control . . . he shall initiate proceedings for control . . . under subsection (a) of this section." Id.

Procedural History

Pursuant to section 811(b), in March 1996, the Drug Enforcement Administration (DEA) requested from the Department of Health and Human Services (HHS) a scientific and medical evaluation of carisoprodol, and a recommendation as to whether it should be controlled. ALJ Ex 1, at 3. In February 1997, however, the U.S. Food and Drug Administration's (FDA) Drug Abuse Advisory Committee concluded that the then-available data did not support controlling carisoprodol. Id.

Thereafter, at the direction of the National Institute on Drug Abuse (NIDA) and the College of Problems of Drug Dependence (CPDD), additional pharmacological studies of carisoprodol's abuse liability were conducted. In the meantime, DEA gathered additional new data on actual abuse and law enforcement encounters involving the drug, as well as other information, which it sent to HHS on November 14, 2005. FDA also acquired new data from the Drug Abuse Warning Network (DAWN), the National Survey on Drug Use and Health

(NSDUH), Florida Medical Examiners Commission reports, FDA's Adverse Event Reporting System, as well as other information from a variety of sources.

On October 6, 2009, HHS concluded its review of the evidence pertaining to the eight factors set forth in 21 U.S.C. 811 and recommended that carisoprodol be placed in schedule IV. GX 6, at 1. Thereafter, on November 17, 2009, DEA issued a Notice of Proposed Rulemaking, which proposed placing carisoprodol in schedule IV. ALJ Ex., at 1 (74 FR 59108). Therein, DEA invited all persons to submit written comments or objections to the proposed rule; DEA also notified "interested persons" of their right to request a hearing. Id. at 2 (citing 5 U.S.C. 556 and 557).

DEA received seventeen comments on the proposed rule; sixteen of the commenters (which included law enforcement officials, medical professionals and state regulators) supported the proposed rulemaking.[1] One entity, Meda Pharmaceuticals, Inc. (Meda), which manufactures the branded drug Soma, objected to the proposed rule on the ground that the "the administrative record does not include substantial and reliable evidence of potential for abuse sufficient to warrant scheduling carisoprodol and because the proposal gives inadequate weight to the negative impact on patient care of scheduling carisoprodol." ALJ Ex. 2, at 3. Meda also requested a hearing. Id. at 1. On March 21, 2010, I granted Meda's request and assigned the matter to the Agency's Office of Administrative Law Judges (ALJ). ALJ Ex. 3, at 2.

Following pre-hearing procedures, an ALJ conducted a hearing on July 6, 8, and 9, as well as on August 3-6, 2010. At the hearing, both the Government and Meda elicited the testimony of witnesses and introduced various documents into evidence. Thereafter, both the

[1] None of the commenters raised any issue as to the various Regulatory Certifications contained in the Notice of Proposed Rulemaking. See 74 FR at 59111. One commenter, which represents wholesale distributors, requested that if the proposed rule is finalized, its effective date be set at 120 days from the date of publication to provide adequate time to comply with various regulations.

Government and Meda filed briefs containing their proposed findings of fact and conclusions of law.

The ALJ's Recommended Decision

On December 8, 2010, the ALJ issued her recommended decision. Therein, prior to discussing the eight "factors determinative of control," 21 U.S.C. 811(c), the ALJ discussed the weight to be given the FDA's findings as to scientific and medical matters. ALJ at 6; see also 21 U.S.C. 811(b). As explained more fully below, the ALJ adopted the Government's argument that the statute "limits the scope of the administrative hearing to those issues outside of the medical and scientific fact-findings of the FDA," ALJ at 11, and concluded that "the plain language and legislative history of § 811(b), federal case law, and [HHS's] process for conducting its administrative review, make clear that Congress intended that the Secretary's scientific and medical fact-findings bind the DEA during the hearing and the subsequent scheduling determination." Id. at 18.

However, the ALJ then noted that "not all of the conclusions that the FDA made in its review are scientific and medical" in nature and that the FDA's conclusions based on data obtained from the Drug Abuse Warning Network (DAWN), the National Survey on Drug Use and Health (NSDUH), and the Florida Medical Examiners/Coroners Reports "could equally fall under the umbrella of law enforcement or science and medicine." Id. at 19-20. The ALJ ultimately concluded that "the data gathered by these sources [was] primarily statistical, and not medical, and [is] therefore capable of review by this agency." Id. at 20. The ALJ thus concluded that FDA's conclusions based on this data are "not binding." Id. Moreover, notwithstanding her statement as to the scope of the hearing, the ALJ allowed Meda to introduce extensive

evidence including expert testimony as to the various scientific and medical matters considered by the FDA.

The ALJ then made extensive findings as to each of the eight section 811(c) factors. With respect to Factor One - the actual or relative potential for abuse - the ALJ first explained that "abuse is using a drug for nonmedical purposes for [its] positive psychoactive effects." Id. at 82. The ALJ then noted the testimony of one of Meda's expert witnesses, who runs a drug treatment center, that he could not recall a single case of a person being treated at his center for dependence on carisoprodol and his opinion that "the data and information presented by the FDA and DEA do not establish that carisoprodol has a potential for abuse similar" to schedule IV controlled substances. Id.

However, the ALJ found "more compelling" data compiled by Meda and the predecessor holders of the New Drug Application for carisoprodol which had been submitted to the FDA's Adverse Events Reporting System (AERS). Id. at 82. This data, which includes reports from consumers and healthcare practitioners, showed that between January 1979 and May 1, 2010, there had been "731 spontaneous adverse event" reports of which eighty-three used such terms as abuse, dependency or withdrawal. Id. at 82-83.

The ALJ further noted that in 2009, FDA required that Meda re-write the drug's label to note the effects of chronic use, that there are "published case reports of human carisoprodol dependence," and that various animal studies indicate the drug has "effects similar to the use of barbital, meprobamate, and chlordiazepoxide," all of which are controlled substances. Id. at 83. The ALJ also noted that Meda eventually accepted the labeling change. Id. at n.42. Based on the AERS data and the drug's label, the ALJ concluded that carisoprodol's "abuse potential is

recognized," and that "the record contains substance evidence of a potential for abuse when carisoprodol is chronically used."

With respect to Factors Two and Three – the scientific evidence of carisoprodol's pharmacological effect and the state of current scientific knowledge regarding the drug - the ALJ noted that "[b]oth the DEA and the FDA relied on animal studies of self-administration, drug discrimination, and physical dependence to support their position that carisoprodol should be classified as a schedule IV drug." Id. at 84. The ALJ then noted the testimony of Meda's Expert that "while the animals reflected behavior patterns with respect to carisoprodol that suggest patterns similar to barbiturates, the limitations of animal studies 'do not provide an adequate basis to make decisions concerning abuse potential in humans,'" and that "'certain drugs will substitute for drugs of abuse without themselves being subject to any significant drug abuse.'" Id. The ALJ, however, then held that "the FDA's conclusions regarding carisoprodol's pharmacology and withdrawal patterns [were] binding on this proceeding." Id.

The ALJ then discussed three different human studies. With respect to the Fraser study,[2] the ALJ noted that Meda's Expert interpreted the results as showing that "ingestions 'did not induce a characteristic barbiturate intoxication pattern . . . , nor did the abrupt withdrawal of carisoprodol reveal any signs of barbiturate-like abstinence' behavior." Id. at 85. However, the ALJ then noted that "the FDA and the DEA found that the subjective and objective effects were similar to those of barbiturates or alcohol and different from those of opiates" and that the drug "has sedative-like effects." Id. Here again, the ALJ found FDA's findings binding on the proceeding. Id.

[2] While both parties and the ALJ cited this study as if it was an exhibit in the case, it was not included in the record forwarded to this Office and there is no indication that it was entered into evidence.

Next, the ALJ discussed the studies Meda had conducted to obtain FDA approval to market a smaller-strength dose. While these studies, which involved 4,000 patients, showed no evidence of diversion, misuse, or abuse, and none of the patients experienced withdrawal following discontinuation of the drug, the ALJ noted that the studies' subjects received only therapeutic doses and did so only "for a period of one to two weeks." Id. The ALJ thus concluded that these trials "did not test the effects of prolonged use of carisoprodol at ingestion levels above the levels for therapeutic use." Id.

The ALJ then discussed a case study by doctors from the Mayo Clinic of a 51-year old man who had taken up to six times the maximum recommended daily dose, which concluded that the case "demonstrates adverse effects of both carisoprodol toxicity and withdrawal." Id. at 85-86. More specifically, the ALJ noted the study's findings that "abrupt discontinuation of high-dose carisoprodol may result in withdrawal symptoms including anxiety, psychosis, tremors, myoclonus, ataxia and seizures," and that "[t]his withdrawal syndrome is likely underrecognized." Id. at 86.

Finally, the ALJ noted the FDA's findings that "carisoprodol possesses sedative properties which may underlie its therapeutic usefulness and its potential for abuse," that "[r]ecent in vitro studies demonstrated that "carisoprodol 'possesses barbiturate-like effects," that the drug "has positive reinforcing effects and [that] its discriminative stimulus effects are similar to other schedule IV drugs such as barbital, meprobamate and chlordiazepoxide." Id. While the ALJ noted that Meda's Expert had challenged the FDA's reliance on an in vitro study, she held again that the FDA's "conclusion is binding on this proceeding." Id. Based on "the totality of the record," the ALJ thus concluded that "the record demonstrates that excessive

carisoprodol use creates similar toxicity and withdrawal symptoms to other schedule IV drugs." Id.

With respect to Factors Four and Five – the history and current pattern of abuse, and the scope, duration, and significance of abuse – the ALJ began by noting the testimony of several law enforcement officials including the head of the DEA Office of Diversion Control, the Executive Director of the Ohio State Board of Pharmacy, and a Special Agent in Charge with the Tennessee Bureau of Investigation, each of whom testified that carisoprodol was being obtained for other than a legitimate medical purpose and being either abused or sold on the street.

The ALJ then discussed data obtained from the National Forensic Laboratory Information System (NFLIS), the National Survey on Drug Use and Health (NSDUH), the Drug Abuse Warning Network (DAWN), Florida Medical Examiners, and the National Poison Data System (NPDS). While noting that the NFLIS data, which showed that carisoprodol was consistently among the top twenty-five drugs being seized during criminal investigations and analyzed by state and local forensic laboratories are "not direct evidence of abuse," the ALJ concluded these data "lead[] to an inference that [the drug] has been diverted and abused." Id. at 88.

As for the NSDUH data, the ALJ noted that data for the years 2004 through 2007 estimate that between 2,525,000 and 2,840,000 million individuals have used carisoprodol during their lifetime for a non-medical reason. Id. at 89. While observing that the yearly estimates "may remain relatively consistent," the ALJ observed that "they are still a significant number of nonmedical uses." Id. However, the ALJ then noted that "these numbers are significantly lower than comparable numbers for the nonmedical use of benzodiazepines." Id.

Next, the ALJ discussed the DAWN data. With respect to the DAWN Emergency Department data, the ALJ noted that these data show that the abuse frequency of carisoprodol "is

similar to that of diazepam, a schedule IV drug," and that the data show an "increasing frequency of nonmedical use emergency department visits associated with carisoprodol." Id. However, the ALJ then noted the credited testimony of another of Meda's expert witnesses that there is a "lack of transparency in the methods used to collect . . . and statistically extrapolate" the data, that without "understanding the nature and extent of the changes in case findings(s) during the last several years, it is impossible to conclusively say what proportion of the increases in DAWN ED national estimates is attributable to changes in methodology versus changes in the actual number of DAWN cases associated with a particular drug," and that "[t]his hinders any effort to interpret" the trends over time. Id. The ALJ thus agreed with Meda's expert that DAWN ED data "may not be the best evidence in this record for concluding that the abuse of carisoprodol is increasing over time." Id.

As for the DAWN Medical Examiner data, the ALJ noted that the "reporting [of] a drug in this reporting system means that the drug need only be implicated or suspected in the death." Id. at 90. Quoting the testimony of Meda's Expert, the ALJ found that "'carisoprodol may not have been the actual cause of death, and it is not possible to conclude that carisoprodol 'abuse' was the cause of death in these cases.'" Id. However, the ALJ noted that the data "showed a link, even if not direct evidence of a cause, between carisoprodol use in combination with other drugs and death in 434 cases of death in 2006." Id.

Turning to the Florida Medical Examiner data, which show that 415 carisoprodol-related deaths occurred in 2008, and an increase of "about 62 percent" in the "total occurrence of carisoprodol/meprobamate in Florida drug abuse deaths," the ALJ again noted the testimony of Meda's Expert that "carisoprodol may not be the cause of death, but rather it may be merely

present in the body at the time of death." Id. However, the ALJ then found that the FDA "determined that carisoprodol was considered the cause of death in 88 cases in 2007." Id.

Next, the ALJ noted that the NPDS data show that in 2007, "'carisoprodol was associated with 8,821 toxic exposure cases, including 3,605 cases in which [it] was the sole drug mentioned,'" and that "[c]ases of individuals treated in health-care facilities because of a major adverse health-outcome total 122 out of the 2,821 single exposure cases." Id. at 91. The ALJ then acknowledged the testimony of Meda's Expert that because the cases are self-reported and "the reporting individual may misidentify the substance during the call to the poison center, 'it [is] impossible to conclude that a mentioned drug was causally implicated in the exposure.'" Id. However, the ALJ also noted the testimony of Meda's Expert that the "'poison center data have some use, but must be interpreted with caution.'" Id.

The ALJ further found that while the "the intentional exposure data" for the years 2006 and 2007 show that the number of deaths attributable to "single exposure cases" had remained at one per year, the number of cases with "major effects went from 105 to 122," and the number of cases with "moderate effects went from 688 to 720." Id. at 91-92. The ALJ thus concluded that the increases in the major and moderate effects cases support the "conclusion that 'individuals are taking carisoprodol in amounts sufficient to cause hazard to their health.'" Id. at 92.

Finally, the ALJ observed that the FDA had "found that data from '2002-2006 indicate that more than 25 percent of patients used the drug [for] longer than one month and 4.3 percent used the drug more than 360 days,'" and that "'[l]onger term use may contribute to increased risks of misuse and abuse.'" Id. The ALJ then noted that she "agree[d] with the FDA's conclusion." Id.

With respect to Factor Six – the risk, if any, to public health – the ALJ again noted the testimony of the head of DEA Office of Diversion Control, the Executive Director of the Ohio State Board of Pharmacy, and the Special Agent in Charge with the Tennessee Bureau of Investigation to the effect that "the failure to schedule carisoprodol poses a great risk to public health." Id. at 92-93. The ALJ further noted the FDA's conclusion that because carisoprodol is metabolically converted to meprobamate, a schedule IV controlled substance, "the public health risks of carisoprodol may be similar to those of meprobamate"; the poison control center data which "show that 'individuals are taking carisoprodol in amounts sufficient to cause hazard to their health'"; and FDA's finding that "'the risks of carisoprodol to the public health are typical of other central nervous system depressants that are controlled'" and that "'[t]hese risks include central nervous system depression, respiratory failure, cognitive and motor impairment, addiction, dependence, and abuse.'" Id. (citations omitted). The ALJ again found that the FDA's conclusions were "binding on this proceeding." Id. at 93.

The ALJ then noted Meda's evidence showing a decline in the number of prescriptions that occurred in four States which have controlled carisoprodol, as well as Meda's contention that controlling the drug would have a chilling effect on the legitimate prescribing of the drug because of the reluctance of physicians to prescribe a controlled substance and that this would be "to the detriment of those patients who would be best treated with carisoprodol." Id. at 93-94. The ALJ found, however, that "anecdotal evidence in this record contradicts this prediction," because one of Meda's Experts testified that if carisoprodol was controlled, he would continue to prescribe it. Id. at 94. The ALJ then found that DEA data showed that controlling other drugs "did not result in physicians ceasing to prescribe" them. Id.

Finally, the ALJ found that "carisoprodol has been implicated in cases of impaired driving, with symptoms consistent with other central nervous system depressants, especially alcohol," and that "[a] Norwegian study also supported this proposition." Id. The ALJ was unpersuaded by Meda's argument "that many uncontrolled drugs have labels warning against driving while taking such drugs," noting that "[i]mpaired driving is a risk to the public health," and thus supports the "conclusion that published scientific reports indicate that taking carisoprodol is associated with risk to the public health." Id.

With respect to Factor Seven – the drug's psychic or physiological dependence liability - the ALJ observed that "[d]ependence includes both physical and psychological dependence." Id. While noting that "there are noncontrolled drugs for which an individual may have a physical dependence," a drug-taker's conduct must be "viewed in total" to determine if the person "has a psychic drive or craving to obtain the drug." Id. at 95. The ALJ then noted that based on various scientific studies, the FDA had "found that carisoprodol has a dependence liability that is similar to that of barbital, a Schedule IV central nervous system depressant, in its dependence potential," and that the FDA's finding was binding on the proceeding. Id. The ALJ also cited the testimony of a DEA witness that carisoprodol is abused by individuals to obtain a "mellow euphoria." Id.

The ALJ also found that two studies had shown that carisoprodol produces "subjective and objective effects" in "human subjects [that] were similar to those of barbiturates or alcohol," the former being controlled substances listed in both schedules III and IV. Id. at 96. The ALJ then noted the testimony of Meda's Expert that if "carisoprodol induced a barbiturate intoxication pattern, [this] could be a possible indicator that carisoprodol possesses barbiturate-like abuse liability." Id.

Finally with respect to Factor Eight – whether carisoprodol is an immediate precursor to a substance already controlled – the ALJ found it undisputed that the drug "is not an immediate chemical precursor or intermediary of a controlled substance." Id.

The ALJ then addressed the three section 812(b) placement factors. With respect to Factor One - whether the drug has a low potential for abuse relative to the drugs in schedule III - the ALJ began by noting the FDA's recommendation (and the concurrence of the National Institute on Drug Abuse (NIDA)), that carisoprodol should be placed in schedule IV. Id. The ALJ found that "[e]mpirical evidence supports the FDA's conclusion," including the evidence that carisoprodol metabolizes into meprobamate, a schedule IV controlled substance," and that various studies support the conclusion that carisoprodol has effects similar to barbiturates, which are schedule III and IV controlled substances. Id. at 96-97. The ALJ also found that notwithstanding that the DAWN ED data, which show that the "abuse frequency of carisoprodol is similar to that of diazepam, a schedule IV drug," "may be overly inclusive," this limitation would not result in "any significant difference in ED visits between the reported drugs." Id. at 98. While acknowledging that the NSDUH data show that "carisoprodol is being abused . . . at a rate significantly less than that of benzodiazepines," the ALJ found that "the NSDUH and DAWN are two distinct studies, both on methodology and measurement, and therefore cannot adequately be compared." Id. at 98-99.

With respect to Factor Two – whether the drug has a currently accepted medical use in treatment in the United States - the ALJ found it undisputed that carisoprodol has been approved by the FDA for the treatment of "acute, painful musculoskeletal conditions." Id. at 99-100. The ALJ thus found that "carisoprodol has a currently accepted medical use in the United States." Id. at 100.

With respect to Factor Three – whether abuse of the drug may lead to limited physical or psychological dependence relative to the drugs in schedule three – the ALJ credited the testimony of two of Meda's experts to the effect that carisoprodol "does not create abuse liability patterns typical of controlled drugs" and that "[t]here does not appear to be any patient 'liking' that would indicate an abuse potential." Id. at 101. The ALJ nonetheless found that "there is substantial evidence in the record based on the animal data, AERS reports, and Mayo Clinic data that carisoprodol produces dependence and withdrawal symptoms similar to other controlled substances in schedule IV." Id. The ALJ further held that "FDA's conclusions regarding the psychological and physiological dependence of carisoprodol [were] binding on this proceeding." Id.

The ALJ thus concluded that substantial evidence supports the controlling of carisoprodol under the eight factors of section 811(c). Id. at 102. The ALJ further concluded that substantial evidence supported the placement of carisoprodol in schedule IV. Id. (citing 21 U.S.C. 812).

Meda filed Exceptions to the ALJ's decision. Thereafter, the ALJ forwarded the record to me for final agency action.

Having considered the entire record, including Meda's Exceptions (which are discussed more fully below), I agree with its contention that the ALJ erred in holding that the FDA's scientific and medical findings are binding on this proceeding. However, because the ALJ allowed Meda to put on extensive evidence as to the scientific and medical matters considered by the FDA, and because, as ultimate factfinder (see 5 U.S.C. 557(b)), I have considered Meda's evidence in deciding whether substantial evidence supports the scheduling of carisoprodol, I conclude that the ALJ's error is not prejudicial. Because I hold that the record as a whole

contains substantial evidence to support the findings required to control carisoprodol and place it in schedule IV of the CSA, I will issue a rule placing carisoprodol in schedule IV.

The ALJ's Ruling on the Binding Nature of the FDA's Scientific and Medical Evaluation

As noted above, "before initiating proceedings . . . to control a drug or other substance," the Attorney General is required to "request from the Secretary a scientific and medical evaluation, and [her] recommendations, as to whether such drug or other substance should be so controlled." 21 U.S.C. 811(b). Congress specified that "[i]n making such evaluation and recommendations, the Secretary shall consider the factors listed in paragraphs (2), (3), (6), (7), and (8) of subsection (c) . . . and any scientific or medical considerations involved in paragraphs (1), (4) and (5) of such subsection.'" Id. The Secretary is directed to provide the Attorney General with her "evaluation and . . . recommendations," which "shall include recommendations with respect to the appropriate schedule, if any, under which such drug or other substances should be listed." Id.

Subsection (b) further provides that "[t]he recommendations of the Secretary to the Attorney General shall be binding as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance." Id. Moreover, "[i]f the Attorney General determines that these facts and all other relevant data constitute substantial evidence of potential for abuse such as to warrant control . . . he shall initiate proceedings for control . . . under subsection (a)," the provision which requires that a rule scheduling a substance "be made on the record after opportunity for a hearing pursuant to the rulemaking procedures prescribed by" 5 U.S.C. 556 and 557.

The ALJ held that "the CSA limits the scope of the administrative hearing to those issues outside of the medical and scientific fact-findings of the FDA." ALJ at 11. According to the ALJ, the "the plain language and legislative history of [sections 811(a) and (b)] and federal case law indicate [that] Congress intended that the Secretary's scientific and medical fact-findings bind the [Agency] throughout the scheduling process." Id. The ALJ further rejected Meda's contention that construing the statute in this manner would deny it a meaningful hearing and render the hearing "largely superfluous," concluding that "Respondent will be afforded the opportunity for a meaningful APA hearing without the opportunity to litigate the factual underpinnings of the [HHS] report." Id.

The ALJ thus rejected Meda's contention that the FDA's findings as to medical and scientific matters are only binding on the Agency's decision as to whether to initiate a scheduling proceeding and that the Secretary's findings are not binding on either the ALJ or the Administrator in evaluating the record of the hearing. Id. at 9-11 (discussing Meda Br. 15-18). As noted above, throughout her consideration of the factors, the ALJ held that she was bound by FDA's findings as to scientific and medical matters and that Meda was not entitled to challenge the Secretary's medical and scientific findings. See, e.g., ALJ at 85-86 (holding FDA's findings as to Factor Two (Section 811(c)) binding notwithstanding Meda's contrary evidence).

I find the ALJ's reasoning confusing,[3] and that she gave insufficient consideration to the most relevant judicial decisions; I therefore reject her legal conclusion. To be sure, the Supreme Court has recognized that "[t]he CSA allocates decision making powers among statutory actors so that medical judgments . . . are placed in the hands of the Secretary," and that the "[t]he

[3]Compare ALJ at 11 (noting that dicta in Reckitt & Coleman, Ltd., v. Administrator, 788 F.2d 22, 27 n.8 (D.C. Cir. 1977), "highlights the inherent ambiguity in the statutory language"), with id. at 18 (holding that "the plain language" of section 811(b) "make[s] clear that Congress intended that the Secretary's scientific and medical fact-findings bind the DEA during the hearing and the subsequent scheduling determination").

structure of the CSA . . . conveys unwillingness to cede medical judgments to an Executive official who lacks medical expertise." Gonzales v. Oregon, 546 U.S. 243, 265 (2006). Yet, the ALJ's sweeping conclusion that this "language supports the inference that the Supreme Court interpreted 811(b) to indicate that those medical judgments are final and not subject to litigation before the DEA," ALJ at 13 (emphasis added), cannot be squared with other provisions of the statute. Moreover, the Court did not decide the issue.

As noted above, upon receiving the Secretary's evaluation and recommendation, the Attorney General is charged with the duty to "determine that these facts and all other relevant data constitute substantial evidence of potential for abuse such as to warrant control." 21 U.S.C. 811(b) (emphasis added). In the event the Secretary's evaluation and the other relevant data constitute substantial evidence such as to warrant control, the Attorney General may then initiate proceedings to control the drug. However, Congress further provided that "Rules of the Attorney General [to control a drug] shall be made on the record after opportunity for a hearing pursuant to the rulemaking procedures prescribed by" the Administrative Procedure Act (APA). 21 U.S.C. 811(a).

Under this provision, a rule may not be "issued except on consideration of the whole record or those parts thereof cited by a party and supported by and in accordance with the reliable, probative, and substantial evidence." 5 U.S.C. 556(d) (emphasis added). Were it the case that the Secretary's findings as to medical and scientific matters are not subject to litigation in the subsequent rulemaking hearing, the only issues left to be litigated would be the drug's "actual" abuse, its "history and current pattern of abuse" and the "scope, duration, and significance of abuse." 21 U.S.C. 811(b). However, an on-the-record hearing (as opposed to notice and comment rulemaking) would hardly be necessary to determine whether the data

proffered by the Agency is adequate to support the findings necessary to control a drug. As the D.C. Circuit explained in Reckitt,[4] if HHS's medical and scientific findings are binding throughout a proceeding, "it is difficult to see what purpose the agency's on-the-record hearing [would] serve[.]"[5]

The ALJ's also found unpersuasive Grinspoon v. DEA, 828 F.2d 881 (1st Cir. 1987). Grinspoon involved a petition to review the Agency's issuance of a final rule placing MDMA in schedule I. 828 F.2d at 882. In Grinspoon, the petitioner raised four different challenges to the Agency's rule. Id. at 882-83. These included, inter alia, that the "Administrator applied the wrong legal standard" because he interpreted the "phrases 'accepted medical use in treatment in the United States,' and 'accepted safety for use . . . under medical supervision'" as meaning "approved for interstate marketing . . . under the" Food, Drug and Cosmetic Act, id. at 884

[4] At issue in Reckitt & Coleman was a rulemaking which rescheduled buprenorphine from schedule II to schedule V, but which designated the drug as a narcotic based on the ground that it is a derivative of thebaine. See 788 F.2d at 22. In a footnote, the Court of Appeals discussed an argument advanced in the brief of a third-party intervenor (which the Department endorsed at oral argument) that the Agency's conclusion could be upheld on the ground that "HHS's initial communication to DEA stated that buprenorphine is a thebaine derivative, and the Act makes HHS's recommendations as to 'scientific and medical matters' binding on the DEA." 788 F.2d 27 n.8 (citing 21 U.S.C. 811(b)). While the court concluded that it was unnecessary to reach the issue, as noted above, it expressed considerable skepticism as to the reasonableness of the view that the Attorney General is bound by the Secretary's finding on a scientific issue notwithstanding contrary evidence presented at a hearing. While the D.C. Circuit's discussion is not binding, it is dictum which the Agency ignores at its peril.

[5] As support for her holding, the ALJ also cited United States v. Spain, 825 F.2d 1426, 1428 (10th Cir. 1987), and United States v. Pastore, 419 F.Supp. 1318 (S.D.N.Y. 1976). As for the ALJ's reliance on Spain, that case addressed the Attorney General's authority under 21 U.S.C. 811(h), which authorizes the "scheduling of a substance in schedule I on a temporary basis [when] necessary to avoid an imminent hazard to the public safety." See 825 F.2d at 1427. Under this provision, the Attorney General is not required to obtain a scientific and medical evaluation from the Secretary before acting. Id. at 148-29. Thus, the case does not address the issue of whether the Secretary's medical and scientific evaluation and recommendations are subject to re-litigation at the hearing. See 825 F.2d at 1427.

Pastore involved a motion to dismiss an indictment which charged various offenses involving the unlawful distribution and obtaining of the controlled substances phendimetrazine and phentermine. See 419 F. Supp. at 1334-35. While the defendants raised various challenges to the Attorney General's decision scheduling these drugs, both drugs were scheduled without a formal on-the-record hearing. Id. at 1346-48. Here again, the case did not address the issue of whether the Agency is bound by the Secretary's finding on a scientific or medical issue in a formal rulemaking proceeding. See id.

(quoting 21 U.S.C. 812(b)(1)(A)), as well as that "the rule [was] based upon incomplete and arbitrary recommendations from the Secretary." Id. at 883.

The First Circuit held that the Administrator had erroneously interpreted the phrases "accepted medical use in treatment in the United States" and "accepted safety for use . . . under medical supervision" as meaning that the drug had not been approved by FDA for interstate marketing. Id. at 891. The Court thus vacated the rule and ordered the Agency to reconsider the scheduling determination. Id.

The Court, however, also addressed the Petitioner's other challenges to the rule, including that HHS had acted in an arbitrary and capricious manner because it "failed to look beyond its own files upon receiving the Administrator's section 811(b) request," that it did not "consult any organization of medical professionals" or FDA's "Drug Abuse Advisory Committee," that it simply rubber-stamped DEA's eight-factor analysis, and that it had failed to forward a letter from NIDA which questioned evidence pertaining to MDMA's abuse potential in animals. Id. at 897. In rejecting the Petitioner's contention, the court explained:

> [T]he HHS recommendation to schedule a substance is not binding and, indeed, serves to trigger an administrative hearing at which interested persons may introduce evidence to rebut the Secretary's scheduling recommendation. Ultimately, of course, responsibility rests with the Administrator, not HHS, to ensure that the final rule rests on permissible legal standards and substantial evidence.

Id. (footnote omitted).

As Grinspoon makes clear, while the Secretary is the expert as to the scientific and medical matters at issue in the scheduling decision, the Attorney General is obligated to conduct a hearing and to consider contrary evidence even as to these issues. The legislative history buttresses this conclusion.[6] As the House Report explains:

[6] Throughout her discussion, the ALJ explained that "the CSA limits the scope of the administrative hearing to those issues outside of the medical and scientific fact-findings of the FDA," that "Congress intended that the

> The procedure which the Attorney General must then follow to control a drug involves rulemaking proceedings on the record after opportunity for a hearing. This provides opportunity for consideration of the views of persons who would be adversely affected by control of a drug, with judicial review available thereafter; however, this administrative proceeding is more streamlined in its operation than the existing procedures under section 701(e) of the Federal, Food, Drug, and Cosmetic Act, so that controls may be established expeditiously where necessary, with full consideration of all factors involved in the decision-law enforcement problems, medical, and scientific determinations, and the interests of parties affected by the decision to control.

H. Rep. No. 91-1444, 1970 U.S.C.C.A.N. at 4589.

The ALJ also reasoned that the FDA's "detailed administrative process [for] making its scientific and medical fact findings suggests that Congress did not intend the DEA to secondarily review those filings." ALJ at 17. Citing a 1999 Hearing Report of the Subcommittee on Oversight and Investigations of the House Committee on Commerce, the ALJ noted that the "'the scientific and medical evaluation process is a complex one which is part of the balancing of the interests of various agencies'" and that the process "may extend over many years, [and] is subject to review by various components of the FDA and interagency review." Id. The ALJ further noted that under two different FDA regulations, Meda could have requested a hearing before the FDA. ALJ at 17-18 n.5; see also id. at 4 n.2.

However, in enacting subsection 811(a), Congress did not bifurcate the hearing between the two Agencies. Rather, it tasked the Attorney General with the responsibility for conducting

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Secretary's scientific and medical fact-findings bind the DEA throughout the scheduling process," that "Respondent will be afforded the opportunity for a meaningful APA hearing without the opportunity to litigate the factual underpinnings of the [HHS] report," ALJ at 11, and that Gonzales "indicate[s] that [the FDA's] medical judgments are final and not subject to litigation before the DEA." Id. at 13.

However, after concluding that Grinspoon does not support Meda and was distinguishable because the Agency had blindly relied on FDA approval as the sine qua non of the "currently accepted medical use" and "accepted safety for use . . . under medical supervision" standards, the ALJ quoted the passage set forth above and observed that "[i]n light of th[e Administrator's] independence, and Meda's opportunity to present evidence relevant to the Administrator's decision, this tribunal would be hard-pressed to conclude that there was "'no opportunity for consideration of the views of persons who would be adversely affected by control of the drug.'" Id. at 16 (quoting H. Rep. No. 91-1444, at 23 (1970)). Yet, she subsequently concluded that "the plain language and legislative history . . . , federal case law, and [HHS's] process for conducting its administrative review, make clear that Congress intended that the Secretary's scientific and medical fact-findings bind the DEA during the hearing and the subsequent scheduling determination." Id. at 18.

the hearing. Moreover, neither the statute nor the legislative history evidences that Congress intended that challenges to the Secretary's scientific and medical findings be litigated in a proceeding before HHS.

In addition, both the statute and the legislative history make plain that Congress was concerned that scheduling proceedings be done in an expeditious manner. For instance, section 811(b) requires that the Secretary submit his report "to the Attorney General within a reasonable time." 21 U.S.C. 811(b) (emphasis added). Likewise, in discussing the hearing provision, the House Report manifests Congress' intent "that controls may be established expeditiously where necessary." 1970 U.S.C.C.A.N. at 4589. The ALJ's suggestion that Meda was required to request a hearing under either 21 CFR 14.172 or 21 CFR 15.1(a), see ALJ at 17 & n.5,[7] runs counter to Congress's manifest interest in the expeditious resolution of proceedings to control a drug.

In its Exceptions, Meda contends that "the ALJ's decision in this proceeding is predicated upon an erroneous belief that Meda had an opportunity to challenge the scientific and medical fact-finding underlying" the HHS recommendation. Meda Exc. at 1. The exception is well taken. Indeed, as set forth in footnote seven above, under both of these provisions, the decision as to whether to grant a hearing is discretionary. Requiring that Meda litigate the medical and scientific findings before an FDA forum would likely add several years of delay, and would raise a host of additional issues, including whether DEA was required to stay its proceeding while the findings were being challenged before an FDA forum, whether those findings are entitled to res

[7] Under 21 CFR 14.172, "[a]ny interested person may request, under § 10.30, that a specific matter relating to a particular human prescription drug be submitted to an appropriate advisory committee for a hearing and review and recommendations. . . . The Commissioner may grant or deny the request." Under 21 CFR 15.1(a), the Commissioner may "conclude[], as a matter of discretion, that it is in the public interest to permit persons to present information and views at a public hearing on any matter pending before the Food and Drug Administration." Notably, under both provisions, the decision as to whether to grant a hearing is within the Commissioner's discretion.

judicata effect if a formal evidentiary hearing was not held, whether the FDA's decision was a final decision triggering the right to judicial review, and likely others.

Also unpersuasive is the ALJ's reasoning that because the FDA's process for evaluating a scheduling request is complex and time-consuming, "Congress did not intend the DEA to secondarily review those findings." ALJ at 17. As the House Report makes plain, in enacting the scheduling provisions, Congress manifested its intention that scheduling proceedings would be done in an expeditious fashion, but with "full consideration of all factors involved in the decision," including the medical and scientific determinations involved in the decision. 1970 U.S.C.C.A.N. at 4589 (emphasis added). The ALJ's conclusion that the medical and scientific findings of FDA are binding and cannot be "secondarily review[ed]" in this proceeding, is contrary to this intent.

Accordingly, consistent with the APA's requirement that the record as a whole must be considered, I hold that, notwithstanding the Secretary's expertise as to the scientific and medical matters, the Agency is (and the ALJ was) obligated to consider Meda's contrary evidence even as to the Secretary's medical and scientific findings and to determine whether substantial evidence supports the finding that carisoprodol "has a potential for abuse," as well as the findings made in support of placing the drug in schedule IV. See 21 U.S.C. 811(a).

However, while the ALJ misconstrued the statute, she did allow Meda to put on evidence to rebut the Secretary's evaluation of the medical and scientific evidence. Because "[t]he Agency, and not the ALJ, is the ultimate factfinder," Reckitt & Colman, 788 F.2d at 26, I conclude that ALJ did not commit prejudicial error. Cf. 5 U.S.C. 706 ("due account shall be taken of the rule of prejudicial error"). Accordingly, a remand is not necessary and I proceed to consider the evidence with respect to the section 811(c) factors.

FINDINGS OF FACT

Since 1959, carisoprodol has been approved for marketing in the United States under the brand name of Soma; the drug, which is also available as a generic drug, is approved by the FDA for the "relief of discomfort associated with acute, painful musculoskeletal conditions." GX 6, at 1 (letter of Howard H. Koh, M.D., Asst. Sec. for Health, HHS, to the Administrator (Oct. 6, 2009)). As noted above, on October 6, 2009, HHS completed its review and recommended that carisoprodol be controlled and placed in schedule IV of the CSA. Id.

FDA made extensive findings as to each of the eight section 811(c) factors. These findings are discussed below,[8] along with additional evidence provided by DEA's witnesses and the testimony and exhibits submitted by Meda.

Factor 1 - Carisoprodol's Actual or Relative Potential for Abuse

The terms "abuse" and "potential for abuse" are not defined in the CSA. See generally 21 U.S.C. 802. However, the legislative history of the CSA explains that a drug or "substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect" based on the following indicators:

> 1. Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or
>
> 2. There is significant diversion of the drug or substance from legitimate drug channels; or
>
> 3. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance; or

[8] Meda argues that the FDA review "is entitled to very little weight" because "DEA counsel did not call any HHS or FDA witness to testify and justify the scientific, medical, and legal basis underlying the HHS recommendation." Meda. Br. 22. However, most of the findings in the FDA's evaluation were supported by citations to publicly available articles, and it is not clear why an FDA witness was required to testify as to the contents of articles which have been published in scientific and medical journals. Moreover, Meda did not seek to subpoena any of the FDA officials who were involved in the review. Finally, while the Government did not call an FDA or HHS witness "to answer questions about the numerous weaknesses in the data," Meda was clearly able to put on an effective challenge to some of the data cited by the Government.

> 4. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, 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, reprinted in 1970 U.S.C.C.A.N. 4566, 4601.

The legislative history also explains that a determination that a substance has "potential for abuse" should not "be determined on the basis of isolated or occasional nontherapeutic purposes." Id. at 4602 (other citation and int. quotations omitted). Rather, "there must exist a substantial potential for the occurrence of significant diversions from legitimate channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or the safety of the community." Id. However, the legislative history also makes clear that the Attorney General is not "required to wait until a number of lives have been destroyed or substantial problems have already arisen before" controlling a drug. Id.

The legislative history further explains that "[i]n speaking of 'substantial' potential the term 'substantial' means more than a mere scintilla of isolated abuse, but less than a preponderance." Id. Thus, evidence that "several hundred thousand dosage units of a drug have been diverted would be 'substantial' evidence of abuse despite the fact that tens of millions of dosage units of that drug are legitimately used in the same time period." Id. Moreover, "[m]isuse of a drug in suicides and attempted suicides, as well as injuries resulting from unsupervised use are regarded as indicative of a drug's potential for abuse." Id.

As the Assistant Secretary noted, "there is no single test or assessment procedure that, by itself, provides a full and complete characterization of a substance's abuse potential, as this is a

complex determination that is multidimensional." GX 6, at 3. Accordingly, in "assessing the abuse potential of a substance, the Secretary considers multiple factors, data sources and analyses," including "the prevalence, frequency and manner of use in the general public and specific subpopulations, the amount of material that is available for illicit use, as well as evidence relevant to populations that may be of particular risk." Id.

The Assistant Secretary further explained that:

> [a]nimal, human, and epidemiological data are all used in determining a substance's abuse potential. Scientifically, a comprehensive evaluation of the relative abuse potential of a substance includes consideration of the drug's receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics and routes of administration, toxicities, assessment[] of the clinical efficacy, safety database relative to actual abuse, clinical abuse potential studies and the public health risks following marketing of the substance. Epidemiological data can also be an important indicator of actual abuse. Finally, evidence of clandestine production and illicit trafficking of a substance are also important factors.

Id. Set forth below is the parties' evidence as to each of the four indicators of carisoprodol's potential for abuse.[9]

1. Use of carisoprodol results in harm to individuals and the public

The FDA found that an evaluation of published case reports and case series, the FDA Adverse Event Reporting System (AERS), and the SAMHSA DAWN databases, show that carisoprodol as currently used raises concerns not only for the health and safety of the users of this substance, but also for the public because of exposure to those who use carisoprodol. More specifically, the FDA found that these sources of information indicate that serious adverse

[9] I have considered Meda's argument that by relying on the four indicators of abuse set forth in the legislative history, the Agency "has improperly attempted to redefine 'abuse' to mean something much broader than what the Committee contemplated (i.e., use for nontherapeutic purposes)." Med. Br. 13. However, as the Assistant Secretary noted, determining a substance's potential for abuse is a complex and multi-dimensional determination which includes an analysis of animal, human, and epidemiological studies, as well as other factors, GX 6, at 3; and the record contains extensive evidence as to the numerous considerations relevant in assessing a drug's abuse potential.

events, including death, drug dependence, drug withdrawal symptoms, and non-intentional and deliberate overdose are related to the abuse of carisoprodol.

The FDA further noted that adverse events have occurred both when carisoprodol is the sole drug of use, as well as when it is used in combination with other drugs, both licit and illicit (polypharmacy). In addition, the use of carisoprodol has been implicated as a factor in vehicle accidents due to driver impairment. The FDA thus concluded that there is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.[10]

Drug Abuse Warning Network (DAWN) Data

The Substance Abuse Mental Health Service's Administration (SAMHSA) administers the Drug Abuse Warning Network (DAWN, 2007; http://dawninfo.samhsa.gov/). DAWN is a national probability survey of U.S. hospitals with emergency departments (EDs) which is designed to obtain information on ED visits in which recent drug use is implicated. The data are gathered from a representative sample of hospital EDs and are weighted to produce national estimates. In addition to the DAWN ED data, DAWN also collects data on drug-related deaths investigated by Medical Examiners and Coroners (ME/C).[11]

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[10] The FDA more fully discussed the data under Factor Four – carisoprodol's history and current patterns of use, and Factor Six – what, if any, risk there is to public health. GX 6, at 3.

[11] According to the FDA's report, DAWN mortality cases now include the following deaths: Completed suicides, Overmedication, Adverse reactions, Accidental ingestions, Homicide by drugs, Underage drinking and Other deaths related to drugs. The FDA further noted that "[t]he mortality component of DAWN is not national in scope, and Medical Examiners or Coroners (ME/Cs) that report to DAWN are concentrated in metropolitan areas." GX 6, at 17. The FDA then acknowledged that because "the report does not represent a scientific sample, results from participating jurisdictions cannot be extrapolated nationally," and that "because participants can vary from year to year, it is not appropriate to compare aggregated death data between years." Id. Moreover, because "[c]ertain jurisdictions within the metropolitan area may not participate in DAWN . . . selected data can not necessarily be generalized to an entire metropolitan area." Id.

FDA further noted that "[a]pproximately half of the carisoprodol-related deaths reported involve the use of meprobamate in combination with carisoprodol" and that "[d]ue to reporting method variability, it is difficult to

DAWN ED Data

According to FDA, many factors can impact the estimates of ED visits, GX 6, at 11; which "are identified through a retrospective review of medical charts." MX 34, at 33 n.13. Individuals (whether patients or drug abusers) who use a drug may visit EDs for a variety of reasons, including treatment of a life threatening adverse event or to obtain a certification of need before entering a formal detoxification program. If multiple drugs are involved, DAWN may not be able to distinguish whether a single drug or the interaction of drugs caused the ED visit. Moreover, while "DAWN tries to capture only drugs that are related to the ED visit and actively discourages the reporting of current medications that are unrelated to the visit[,] . . . it is not possible, given the limitations of medical record documentation, to eliminate completely the reporting of current medications." MX 34, at 33.

In addition, DAWN defines "nonmedical use" as "use that does not meet the definition of medical use." Id. Under this definition, "nonmedical use of pharmaceuticals includes taking more than the prescribed dose of a prescription pharmaceutical . . . ; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription" pharmaceutical. Id. Because of "the limitations of medical record documentation, [DAWN has] concluded that distinguishing misuse from abuse reliably is not feasible." Id. n.13.

Selected data from DAWN for 2004 - 2007 are shown in Table 1 below. These data

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determine if both drugs were taken in combination or if meprobamate was present in the deceased as a result of carisoprodol metabolism." Id. Finally, FDA noted that "[t]he reporting of carisoprodol found by the ME/C following a post mortem examination does not necessarily imply that carisoprodol was the ultimate cause of death . . . , only that it was identified by the ME/C as involved in the death," and that "[v]ery few deaths from 2003 and 2004 involve the use of carisoprodol by itself and are consistent with other data indicating that carisoprodol is used most often in combination with a variety of other agents." Id. at 18. Because of the numerous limitations with this data, I give no weight to the DAWN ME/C data.

show an increase in the frequency of nonmedical use ED visits associated with carisoprodol. More specifically, in 2004, DAWN estimated that there were 14,736 ED visits related to the nonmedical use of carisoprodol, and that in 2007, there were 27,505 nonmedical ED visits related to the nonmedical use of the drug. However, according to SAMHSA, the increase from 2004 through 2007 did not reach statistical significance. GX 6, at 12. Accordingly, the data do not support a finding that the rate of abuse of carisoprodol is increasing.

The data do, however, support a finding that carisoprodol is resulting in ED visits at a level comparable to that of diazepam, a benzodiazepine and schedule IV controlled substance. As Table 1 shows, in 2004 there were an estimated 15,619 ED visits related to diazepam.[12]

Table 1: Selected Pharmaceutical ED Visits (nonmedical use): 2004 - 2007 from DAWN [Data output 08/02/2008]

	Estimates			
Selected Drugs	**2004**	**2005**	**2006**	**2007**
Carisoprodol	14,736	20,082	24,505	27,128
Cyclobenzaprine	6,183	7,629	7,142	6,197
Diazepam	15,619	18,433	19,936	19,674

By dividing the number of ED visits by the number of prescriptions, FDA calculated "abuse frequencies" for carisoprodol; cyclobenzaprine, a non-scheduled muscle relaxant; and diazepam, which is also prescribed for its muscle relaxant properties. These calculations, which are found in Table 2 below, show that the "abuse frequency" of carisoprodol is in the same range as diazepam and greater than that of cyclobenzaprine. More specifically, even in 2004, the carisoprodol rate was 15.1 ED visits per 10,000 prescriptions, while diazepam's rate was 12.5. By contrast, cyclobenzaprine, another skeletal muscle relaxant had a rate of 4.1 ED visits per 10,000 prescriptions. Most significantly, even in 2004, and before the increase in the estimates

[12] In 2007, DAWN ED carisoprodol visits also accounted for an increasing percentage of the nonmedical use ED visits associated with skeletal muscle relaxants, increasing each year from 59 percent in 2004, to 70 percent in 2007.

of carisoprodol-related ED visits, carisoprodol had a greater frequency of ED related visits than diazepam.

Table 2: Frequency of DAWN ED Visits (nonmedical use) per 10, 000 Rx for Carisoprodol, Cyclobenzaprine and Diazepam (2004 - 2007).

Selected Drugs	2004	2005	2006	2007
Carisoprodol	15.1	19.7	22.9	22.6
Cyclobenzaprine	4.1	4.61	4.1	3.3
Diazepam	12.5	14.5	15.0	14.1
Data derived from proprietary SDI data. SDI Vector One®: National, Years 2002-2007, Data Extracted April, 2008 File: VONA 2008-517 4-15[13]				

Carisoprodol has been reported as a primary or sole drug of abuse in DAWN only since 2006. According to the 2006 DAWN data, there were an estimated 24,505 ED visits related to carisoprodol, of which it was reported as the sole drug in 21 percent of the cases. This is consistent with the FDA's finding that the majority of the cases published in the scientific literature report that carisoprodol abuse has primarily been a component of multi-drug abuse.

FDA reviewed DAWN data and found that the drugs most frequently used in combination with carisoprodol that resulted in ED visits were opioids (hydrocodone, oxycodone), benzodiazepines (alprazolam, diazepam, clonazepam), alcohol, and illicit drugs (marijuana, cocaine). Table 3 below sets forth the respective levels of carisoprodol ED visits related to single use and as a component of multi-drug use.

Table 3: Estimated Nonmedical Use - Carisoprodol ED Visits from DAWN 2006, as Sole

[13] According to FDA, SDI's Vector One™ National (VONA) measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. GX 6, at 13 n.7. Information on the physician's specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available. Id.

The Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Id. Vector One receives over 1.8 billion prescription claims per year, representing over 150 million unique patients. Id. The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the United States, and represents approximately half of retail prescriptions dispensed nationwide. Id. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Id.

Drug and in Combination with Other Drugs

All Patients			Females only			Males only		
Drug	#	%	Drug	#	%	Drug	#	%
Total Carisoprodol	24,505		Total Carisoprodol	14,219	42%	Total Carisoprodol	10,286	58%
Carisoprodol single-drug	5,055	21%	Carisoprodol single-drug	3.870	27%	Carisoprodol single-drug	1,185	12%
Carisoprodol multi-drug	19,450	79%	Carisoprodol multi-drug	10,349	73%	Carisoprodol Multi-drug	9,101	88%

Information received from SAMHSA on June 18, 2008.

FDA also found that although carisoprodol is approved for short term use (≤3 weeks), SDI Vector One data from 2002-2006[14] show that more than 25 percent of patients used the drug for longer than one month, and 4.3 percent used the drug for more than 360 days. GX 6, at 15. FDA concluded that longer term use may contribute to increased risks of misuse and abuse. Id.

MEDA's Evidence Regarding the DAWN Data

Meda offered the testimony of Mr. Nabarun Dasgupta as an expert witness in epidemiology and pharmacoepidemiology. MX 173; Tr. 628. Mr. Dasgupta offered a lengthy critique of the DAWN ED data and opined that "the DAWN ED data are subject to constraints that limit their potential reliability for use in scientific research and public health policy." MX 173, at 3.

More specifically, Mr. Dasgupta criticized the sampling methodology used by DAWN, noting that DAWN uses an oversample of hospitals in select metropolitan areas and a sample of hospitals from the rest of the country and that "[t]he number of hospitals sampled is relatively small compared to the national estimates that are extrapolated from the sample." Id. Mr. Dasgupta noted that for the year 2007, "207 hospitals submitted provided data on 300,983 drug

[14] See Table 6 from the OSE "Duration of Use Analysis" for Soma (NDA 11-792) dated June 27, 2007.

related ED visits . . . which resulted in a national estimate of 3,998,228 drug-related ED visits." Id. at 3-4. Mr. Dasgupta further stated that "[t]he location of all hospitals participating . . . is not disclosed due to privacy reasons," and that "the number of hospitals can change post hoc in the published annual report tables." Id. at 4. As support for the latter assertion, Mr. Dasgupta cited the 2005 and 2006 annual reports; however, only one of these (the 2006 report) was submitted for the record.

Later in his testimony, Mr. Dasgupta asserted that "[o]nce the cases in the participating hospitals are counted, DAWN applies statistical methods to extrapolate to a 'national estimate,'" and that each case is given "a weight from 1 to 60 to arrive at the national estimates," and that while it is "routine to describe how weights are derived," DAWN does not "completely describe the process." Id. at 14. Mr. Dasgupta also explained that while such factors as "'non-response,' missing data, hospital size, physical location, whether it is an academic training hospital, and other factors are accounted for in the weight, . . . the method for doing this is not published." Id. Mr. Dasgupta concluded that "the credibility of the national DAWN data . . . hinges on the statistical methods employed to analyze the sample data, but SAMHSA does not publicly disclose the current methods. We do not know how the weights of the individual hospitals are being applied, and we do not know what impact the extrapolations may be having on the reported national estimates." Id. Mr. Dasgupta thus opined that "[t]he lack of information provided by DAWN concerning its statistical extrapolation methods hinders interpretation and hence limits the weight that can be given the DAWN national estimates." Id. at 14-15.

On examination by the ALJ, Mr. Dasgupta was asked if, "within the community of epidemiologists, . . . the DAWN ED national estimation [is] still relied upon?" Tr. 652. Mr. Dasgupta replied that "[t]he DAWN ED data are important to look at," and that "others would

agree . . . in that it sets . . . it's the data that is used for policy making." Id. Mr. Dasgupta then asserted that "[f]rom a scientific perspective, it doesn't carry much weight." Id. However, DAWN ED does not purport to be anything other than an estimate, and Mr. Dasgupta's testimony suggests that epidemiologists still consider the estimates sufficiently reliable to make policy decisions.

Moreover, Mr. Dasgupta generally did not identify what practices (including what level of disclosure) the field of epidemiologists considers to be necessary to establish the validity of a methodology and the statistical methods used to extrapolate the data to develop a national estimate. While Mr. Dasgupta's criticisms of the DAWN ED data may be based on the generally accepted standards of epidemiology, in the absence of evidence establishing those standards, there is no basis for concluding that his criticisms of DAWN ED data reflect those of the community of epidemiologists rather than his personal opinion.

Mr. Dasgupta further asserted that the scientific validity of the data "is questionable" because it "does not conform with the FDA's published guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessments." MX 173, at 4-5. According to Mr. Dasgupta, this "call[s] into question whether DAWN ED data should be used by FDA and FDA-regulated entities for post-marketing surveillance." Id. However, Mr. Dasgupta did not identify in what respect DAWN does not comply with the FDA's guidance. See id. Nor is it clear why compliance with the FDA's guidance is necessary to establish that the DAWN ED data, which is only an estimate, is not sufficiently reliable to support a finding that carisoprodol "has a potential for abuse." 21 U.S.C. 811(a)(1)(A).

Mr. Dasgupta's next criticism was that the reporters of DAWN ED data "may identify an ED visit as a DAWN case even if the patient has a valid prescription for the drug(s) mentioned in

the ED chart and is taking the drug(s) for therapeutic purposes." Id. at 5. Mr. Dasgupta noted that "[w]hile Reporters are trained on selecting cases, no published studies have evaluated the consistency between Reporters or between hospitals, or over time." Id. Mr. Dasgupta also noted that this "calls into question the reliability of reporting across sites, given the lack of published validation of the consistency between Reporters at different sites." Id.

Mr. Dasgupta further noted that "there has been a concerted effort by SAMHSA and the contractor to improve [the] selection of cases, [which is] aimed at identifying more ED visits for inclusion." Id. at 5-6. Mr. Dasgupta stated that because there has been "no public documentation of this process," it is not clear if "the increases in cases over time is due to better case finding or due to increases in the underlying sociobiologic phenomena that give rise to DAWN cases." Id. at 6. According to Mr. Dasgupta, "it is impossible to conclusively say what proportion of the increases in DAWN ED national estimates is attributable to changes in methodology versus changes in the actual number of DAWN cases associated with a particular drug" and "[t]his hinders any effort to interpret the meaning of time trends." Id.

On examination by the ALJ, Mr. Dasgupta testified that this, i.e., the increase "attributable to enhanced case-finding versus [that] attributable to the underlying actual abuse . . . is something that is routinely looked at in epidemiologic studies." Tr. 657. He also suggested that in such circumstances, "a validation study" would be done to determine how well those persons who review the case files were doing. Id. at 658. However, even acknowledging the validity of this criticism, the FDA's recommendation stated that the increase in the estimates of carisoprodol-related ED visits between 2004 and 2007 was not statistically significant.

Mr. Dasgupta also observed that "DAWN has acknowledged the difficulty in identifying cases of abuse" because of the limitation of medical record documentation. Id. at 7. As Mr.

Dasgupta observed, because DAWN defines "nonmedical use" to include a variety of scenarios beyond misuse/abuse, "ED visits counted as 'nonmedical use'" by DAWN "do not necessarily represent cases of abuse as that term is commonly understood," and as "used for purposes of scheduling." Id. at 9-10.

Mr. Dasgupta also noted that "[a]lthough current medications unrelated to the visit are not supposed to be recorded, distinguishing medications that pertain to the ED visit from those that do not requires a complex toxicological determination," which hospitals may not conduct "in the interest of providing expedient medical care." Id. at 10. Mr. Dasgupta stated that differences in how toxicology testing is conducted at different hospitals "may influence whether a drug is detected," and that "the simple presence of a drug in toxicology results is not sufficient to implicate its involvement in an ED visit." Id. at 12. He further noted that "it is highly probable that to some extent the determination of the involvement of unrelated medications may be inherently subjective, [and may] vary between Reporters," who have different training and experience.[15] Id. at 10. However, Mr. Dasgupta then opined that "drugs are most often identified by patient self-reporting," that "[o]nly a small percentage is confirmed by toxicology tests," and that therefore, "DAWN data are subject to all of the uncertainties and potential misidentifications associated with self-reporting."[16] Id. at 13.

[15] Mr. Dasgupta also testified that the DAWN data may be affected by diagnostic suspicion bias in that DAWN reporters may have become sensitized by news reports or other information as to the abuse of a particular drug, and therefore, may over-report such cases. MX 173, at 12. However, Mr. Dasgupta produced no evidence as to the existence of this phenomenon among DAWN reporters either generally or with respect to carisoprodol.

[16] Mr. Dasgupta further noted that DAWN may at times impute data when data is missing from certain hospitals. MX 173, at 18-19. While Mr. Dasgupta suggested that this practice is of "questionable validity," id., this is not the same as saying that this practice is not generally accepted by experts in the field. Indeed, on examination by the ALJ, Mr. Dasgupta testified that "it is valid to use imputation methods to fill in missing data, but it's a very, very sensitive issue that needs to be done carefully." Tr. 669. Mr. Dasgupta then stated that "[t]here are three, four, maybe five major ways in which imputation is done in epidemiology to fill in missing data like these, and the choice of which of those imputation methods . . . can very strongly influence your results," that "the onus is on the researcher to show that those assumptions have been met and that the method selected is the appropriate one," and that "if there is kind of [a] referenced imputation[,] it's odd to not see those kinds of descriptions on which statistical

As explained above, DAWN explicitly recognizes the limitations inherent in medical record documentation. Moreover, even crediting Mr. Dasgupta's criticisms, as even he recognized, "[t]he DAWN ED data are important to look at" and "it's the data that is used for policymaking." Tr. 652. The DAWN ED data provide only an estimate; the data constitute just one of many pieces of evidence which support the conclusion that persons are taking carisoprodol "in amounts sufficient to create a hazard to their health."

FDA Adverse Event Reporting System (AERS) Data[17]

As noted above, FDA also reviewed the AERS data and found that through June 2007, there were a total of 472 reports related to potential carisoprodol abuse, including 48 reports identifying dependence and 19 identifying withdrawal syndrome. GX 6, at 15. In the majority of cases, multiple drugs were used, but there are 61 unique reports where carisoprodol was the only suspect drug. Id.

Meda's Chief Medical Officer (CMO) provided more up-to-date data. In his written direct testimony, MEDA's CMO stated that "MEDA's database contains a total of 731 spontaneous adverse events for carisoprodol from January 1979 through May 1, 2010," of which "only 83 reports included the terms abuse, dependency, or withdrawal." MX 171, at 10. MEDA's CMO further noted that in the five-year period of 2005-2009, more than 54 million prescriptions, totaling nearly four billion tablets of carisoprodol, were dispensed. Id. at 11.

While the AERS data appears relatively small when compared with the total number of

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imputation method is used." Id. at 669-70. However, Respondent produced no evidence that the use of imputed data has affected the DAWN data for carisoprodol.

[17] The Adverse Event Reporting System (AERS) is a computerized database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. GX 6, at 15. The FDA receives adverse drug reaction reports from manufacturers as required by regulation. Id. Health care professionals and consumers send reports voluntarily through the MedWatch program, which become part of a database; the database complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. Id.

prescriptions, as explained in footnote fifteen, this data is obtained from health care professionals and consumers, both of whom voluntarily submit the reports. As FDA notes, it "does not receive all adverse event reports that occur with a product" as "[m]any factors can influence whether or not an event will be reported." FDA, Adverse Events Reporting System, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrug Effects/default.htm. Accordingly, "AERS cannot be used to calculate the incidence of an adverse event in the U.S. population." Id. Indeed, the voluntary nature of the reports suggests that they are likely to under-represent the actual number of adverse events.

Florida Medical Examiners Commission Data

In 2008, Florida's medical examiners reported 8,556 drug-related deaths (whether the drug was the cause of death or merely present) through toxicology reports submitted to the Medical Examiners Commission. GX 7, at 11. The presence of carisoprodol and/or its metabolite, meprobamate, was found in 415 deaths (5 percent of the drug related deaths). Id. In 84 of these deaths (20%), carisoprodol was determined to be the cause of death. Id. The following table lists, for the years 2003 through 2008, the number of deaths in which carisoprodol and meprobamate were found in toxicology testing and the number of deaths in which carisoprodol and meprobamate were found to be a cause of death.

Table 4: Florida Medical Examiner's Data 2003-2008

Year	Drugs Found in Body	Total Occurrences	Cause (% total)	Present	% Change from prior yr
2003[18]	Carisoprodol/Meprobamate	208	45 (22%)	163	ND
2004	Carisoprodol/Meprobamate	289	81 (28%)	208	39%
2005	Carisoprodol/Meprobamate	314	96 (31%)	218	9%
2006	Carisoprodol/Meprobamate	313	74 (24%)	239	-0.3%
2007	Carisoprodol/Meprobamate	337	88 (26%)	249	8%
2008	Carisoprodol/Meprobamate	415	84 (20%)	331	23%

Id.; see also GX 7, at 11.

With respect to this data, Mr. Dasgupta stated that "[t]he presence of a drug in the body does not establish it as a cause of death" or necessarily "indicate drug abuse." MX 173, at 23. As for the first contention, the data recognizes as much as it differentiates between those instances in which toxicology testing established that carisoprodol/meprobamate was present in a body and those in which a medical examiner concluded that the ingestion of carisoprodol or meprobamate was a cause of death. Likewise, while a drug's presence in the body does not necessarily establish that the person was engaged in "drug abuse," it nonetheless is an indicator of drug abuse, especially where the deaths were found to be caused by an overdose.

Mr. Dasgupta further concluded that because the data combines carisoprodol and meprobamate, "it is not possible to determine . . . which drug . . . was a cause of death." Id. at 23. However, carisoprodol metabolizes into meprobamate, and other data in the record (more specifically, the NSDUH data, see Table 7) indicates that more than eleven times as many persons have engaged in the nonmedical use of carisoprodol than have engaged in the nonmedical use of meprobamate. This supports the conclusion that the great majority of the Florida Medical Examiner cases in which carisoprodol/meprobamate was determined to be a

[18] Carisoprodol was scheduled as C-IV in Florida in July 2002, but was not tracked until 2003. GX 6, at 18.

cause of death are attributable to carisoprodol.[19]

Finally, Mr. Dasgupta asserted that the Florida data shows that "the proportion of total fatal overdose occurrences . . . has generally been decreasing annually since 2005." Id. at 24. However, it is doubtful that this change is statistically significant, and even if it is, the data still show that a significant and disturbing number of persons have died from carisoprodol overdoses and are dying each year in this State alone.

NATIONAL POISON DATA SYSTEM

Data from the National Poison Data (NPDS), formerly known as the Toxic Exposure Surveillance System of the American Association of Poison Control Centers (AAPCC), show that carisoprodol products are involved in a number of toxic exposures (Table 5). Some of these carisoprodol exposures led to major adverse health outcomes (Table 6). For example, in 2007, carisoprodol was associated with 8,821 toxic exposure cases, including 3,605 cases in which it was the sole drug mentioned. A total of 122 of the 2,821 single exposure cases, which were treated in a health-care facility, had a major adverse health outcome.

Table 5: Carisoprodol exposures data from National Poison Data System (NPDS)

	2003	2004	2005	2006	2007
Case Mentions	8,248	8,765	8,613	8,187	8,821
Single Exposures	-------	------	------	3,515	3,605

Note: Single exposure data is not available prior to 2006.

Table 6: Serious adverse health outcomes in carisoprodol exposures cases who were treated in health care facilities.

	2003	2004	2005	2006	2007

[19] Mr. Dasgupta also raised the possibility that the Florida Medical Examiner data is subject to diagnostic suspicion bias. MX17, at 23. Again, this is simply speculation.

Treated in Health Care Facility*	6,617	7,032	7,501	2,687	2,821
Deaths	28	30	18	1	1
Major Effect**	406	468	525	105	122
Moderate Effect***	1,710	1,882	1,953	688	720
Total	2,144	2,878	2,496	794	843

*The data for 2006 and 2007 are from single exposure cases.

**Major effect: the patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement

***Moderate effect: the patient developed signs or symptoms as a result of the exposure that were more pronounced, more prolonged or more systemic in nature than minor effects.

Regarding the NPDS data, Mr. Dasgupta acknowledged that the persons who answer the calls to the regional poison centers "are nurses, pharmacists, and physicians who have been trained in medical toxicology and are instructed on the proper ways of completing case report forms in a systematic manner" and that the data collection software has "[a]n extensive data quality assurance process." MX 173, at 29-30. Mr. Dasgupta then stated that there is the "potential misidentification of the substance during the initial call to the poison center" and that researchers have "determined that, for some drugs, 25-30% are misclassified during the first call." Id. at 30. However, Meda did not provide this research and Mr. Dasgupta did not provide evidence as to what the rate of misclassification is for carisoprodol. He then opined that the self-reporting and (apparently the lack of toxicology test results) showing the "presence and levels of drug . . . make it impossible to conclude that a mentioned drug was causally implicated in the exposure." Id.

Mr. Dasgupta also maintained that "the single exposure data presented by DEA combines single-entity carisoprodol and carisoprodol/aspirin combination products." Id. at 31 (citing Meda Ex. 63).[20] However, as the data for 2007 show, even if single entity and combination

[20] As support for this assertion, Mr. Dasgupta cited the 2008 annual report (MX 63); however, the above tables do not include data for that year.

products should not be counted together, the amount of case mentions and single exposures attributable to combination products is a small fraction of both the case mentions (163 v. 8658) and single exposures (69 v. 3536) attributable to single entity products. See MX 64, at 1020, 1026.

Mr. Dasgupta also criticized the use of the NPDS data because the intentional exposures data includes suicide attempts and accidental pediatric exposures. MX 173, at 34. However, the Senate Report, which accompanied the CSA's enactment, expressly stated that "[m]isuse of a drug in suicides and attempted suicides, as well as injuries resulting from unsupervised use are regarded as indicative of a drug's potential for abuse." S. Rep. 91-613, 1970 U.S.C.C.A.N., at 4602. Thus, contrary to Mr. Dasgupta's understanding, the fact that Table 6 includes suicides, "suicide attempts," and "accidental pediatric exposures," see MX 173, at 34; does not reduce the data's probative value in assessing carisoprodol's abuse potential.

Mr. Dasgupta criticized Table 6 because it "purports to show 'serious adverse health outcomes in carisoprodol exposure cases,'" but "[i]ntentional exposure cases can also include associated medical outcomes that are not serious." Id. at 32. Mr. Dasgupta further asserted that "[t]he DEA Review does not present enough detail concerning methodology to determine what type of cases were included in Table [6]." Id.

However, it is apparent that Table 6 simply replicates the NPDS's classification of carisoprodol incidents by the severity of the outcome. See MX 64, at 940-41, 1020, 1026 (2007 report). Moreover, even if single entity and combination carisoprodol products should not have been added together, the number of cases attributable to combination products is a small fraction of those attributable to single entity products (15 v. 705 moderate effects outcomes, 2 v. 120 major effect outcomes, and 0 v. 1 death). Compare id. at 1020, with id. at 1026.

2. Is there significant diversion of carisoprodol from legitimate drug channels?

The NFLIS Data

Current data shows that there is significant diversion of carisoprodol from legitimate drug channels. Data collected by DEA establishes that carisoprodol has been seized from persons engaged (and places used) in illegal activities involving other controlled substances, including diazepam, marijuana, cocaine, methamphetamine, codeine, and hydrocodone. DEA has found carisoprodol present during the execution of search warrants at residences, offices, and pharmacies. According to data retrieved from DEA's National Forensic Lab Information System (NFLIS) database, which includes data on samples analyzed by DEA laboratories (STRIDE), as well as state and local forensic laboratories,[21] since 2000, carisoprodol has consistently ranked in the top 25 of the drugs most frequently seized and identified by state and local forensic laboratories during the course of criminal investigations.

In terms of the number of seizures, in 2008, NFLIS reported 4,291 identifications of carisoprodol, thus ranking it above such controlled substances as codeine, psilocin, lorazepam, MDA, hydromorphone, and methylphenidate. MX 53, at 9. In 2007, NFLIS reported 4,420 identifications of carisoprodol, thus ranking it above such controlled substances as phencyclidine (PCP), psilocin, buprenorphine, MDA, methylphenidate, ketamine, lorazepam, and hydromorphone. MX 54, at 7. Because the primary focus of law enforcement agencies is on investigating the unlawful distribution of controlled drugs, the incidents in which carisoprodol has been found during law enforcement seizures supports a finding that the drug is being abused and diverted. Moreover, because carisoprodol is not controlled in most States, there is reason to believe that many laboratories may not report those incidents in which they have identified a

[21] Participating state and local laboratories handle 88% of the nation's 1.2 million analyses of state and local drug cases.

substance as carisoprodol. GX 9, at 3.

Mr. Dasgupta opined that the NFLIS data are of "limited utility for making public health decisions." MX 173, at 26. While he acknowledged that carisoprodol has been among the top twenty-five drugs analyzed, Mr. Dasgupta explained that "[t]he likelihood of a particular sample being analyzed is substantially affected by the prosecutor's perceptions of the available criminal charges, as well as politics, prosecutorial priorities, and bureaucratic influences." Id. at 25. Mr. Dasgupta then noted that "[p]rosecutors in states where carisoprodol is a controlled substance would be more likely to submit a sample to NFLIS for identification,[22] as the state-level scheduling would be more likely to result in a stiffer criminal penalty," and that "[f]orensic laboratory data from these states may be an artifact of state-level scheduling because more suspected carisoprodol samples may be sent for analysis once a controlled substance criminal charge is potentially available in a particular state." Id. at 26. As Mr. Dasgupta noted, only seventeen States have controlled carisoprodol. Id. n.7.

This argument, however, actually supports the Government's view that many laboratories do not report carisoprodol that is seized during criminal investigations, and thus the drug is being diverted at even greater levels than the NFLIS data suggests. According to U.S. Census data, of which I take official notice, the seventeen States, which have controlled carisoprodol, have a total population of approximately 108 million and thus comprise only 35% of the national population.[23] See Appendix A. This suggests that carisoprodol would likely rank substantially

[22] Contrary Mr. Dasgupta's understanding, drug samples are not submitted "to NFLIS for identification." MX 173, at 26. Rather, NFLIS collects reports of drugs items which have been seized and analyzed and identified as a drug by a forensic laboratory. However, I agree with Mr. Dasgupta's opinion that if a criminal charge is not available in a State, it is less likely that evidence which looks like carisoprodol tablets will be sent to a lab for analysis and subsequently reported to the NFLIS.

[23] Pursuant to 5 U.S.C. 556(e), Meda "is entitled, on timely request, to an opportunity to show the contrary." In the event Meda disputes the census data, it may file a motion for reconsideration within fifteen days of the date of service of this rule, which shall begin on the date of mailing.

higher in the NFLIS data were it controlled nationally.

The testimony of various officials further supports a finding that carisoprodol is being diverted. The Deputy Assistant Administrator of DEA's Office of Diversion Control testified that carisoprodol was being distributed in combination with narcotic drugs and benzodiazepines through internet schemes in which patients were issued prescriptions by physicians they never saw and could simply order the drugs through a website. GX 9, at 2-3; Tr. 343-44. As several courts have recognized, the dispensing of controlled substances in this manner is a violation of 21 U.S.C. § 841(a)(1). See United States v. Nelson, 383 F.3d 1227, 1231-32 (10th Cir. 2004); United States v. Smith, 573 F.3d 639, 657-58 (8th Cir. 2009); United States v. Fuchs, 467 F.3d 889 (5th Cir. 2006). The Deputy Assistant Administrator also noted that "DEA investigations reveal that thousands of customers throughout the United States seek carisoprodol, either alone or, most frequently, in combination with controlled substances from pain clinics, physicians, and from illicit street dealers." GX 9, at 3.

A Special Agent in Charge with the Tennessee Bureau of Investigation, who oversees drug enforcement responsibilities in twenty-eight of the State's counties and who was formerly Coordinator of the Tennessee Drug Diversion Task Force, testified that in his experience, "carisoprodol has been used for non-medical purposes and illicitly distributed in circumstances that are similar to the non-medical use and illicit trafficking in controlled substances such as oxycodone, hydrocodone, and alprazolam. Law enforcement investigations have revealed that many Tennesseans seek carisoprodol, either alone or, most frequently, in combination with controlled substances from pain clinics [and] physicians," who "conduct little or no physical examination of the patients" and who "issue prescriptions for the specific drugs requested by the 'patients.'" GX 10, at 3-4. The official also related that carisoprodol is being sold on the street.

Id. at 4.

The official also testified that "carisoprodol abuse has been implicated in many overdose events in Tennessee including overdose fatalities," and that reports from the State's medical examiner "from 2006 through 2008" show that carisoprodol has been "associated with approximately 100 deaths." Id. at 3, 5. This official further stated that "[i]n the majority of these cases[,] carisoprodol is seen in combination with a 'cocktail' of other drugs[,]" such as "oxycodone or hydrocodone." Id. at 5.

The Executive Director of the Ohio State Board of Pharmacy, who has worked as a pharmacist as well as held oversight/investigatory positions at the Board, testified that he has "personally investigated cases involving carisoprodol," and that "carisoprodol has been abused in the State of Ohio for more than 20 years." GX 8, at 3. The official testified that he was "aware from [his] experience that many abusers of narcotics and other drugs abuse carisoprodol to mellow the effect of the narcotics or other drugs." Id.

The official further testified that under Ohio law, pharmacies are required to report the dispensing of any controlled substance as well as carisoprodol. He then related that he had run a search of the Ohio prescription reporting system and found that carisoprodol "is always prescribed in combination with an opiate, a benzodiazepine, or both." Id. at 4-5. Moreover, "even though . . . the use of a muscle relaxant such as carisoprodol in conjunction with an opiate and a benzodiazepine is rarely clinically indicated,"[24] the official "found that our top ten prescribers of this 'trinity' have prescribed this combination [of drugs] to a range of 140 [to]

[24] On cross-examination, the official explained that both carisoprodol and benzodiazepines have muscle relaxant and anti-anxiety effects, and that prescribing both drugs simultaneously "is duplication of therapy," which is rarely warranted. Tr. 464-65.

1,376 patients." Id. at 5. The official further found that "many patients received carisoprodol from multiple prescribers," that during 2009, the top ten patients "received prescriptions from 8 [to] 13 different prescriptions," and that these "patients received between 1,020 [and] 1,863 days' supply" of the drug during the "365 day period." Id. However, carisoprodol is indicated only for short-term use of up to two to three weeks, "because adequate evidence of effectiveness for more prolonged use has not been established and because acute, painful musculoskeletal conditions are generally of short duration." MX 6, at 2 (prescribing information). As the official concluded, these statistics provide evidence of improper prescribing by physicians, as well as doctor shopping and over-utilization by patients, and show that "carisoprodol is a drug of abuse in Ohio." Id.

3. Non-medical use of carisoprodol

Review of the currently available data and other information shows that individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances. More specifically, the National Survey on Drug Use and Health (NSDUH)[25] data show that from 2004 through 2007, between 2.5 and 2.8 million persons admitted to having used carisoprodol for a non-medical purpose during their lifetime.[26] As Table 7 below shows, in 2007, approximately 2.7 million persons have at some point engaged in the non-medical use of carisoprodol. This figure is more than eleven

[25] The NSDUH is an annual survey sponsored by SAMHSA that obtains information on nine different categories of illicit drug use: use of marijuana, cocaine, heroin, hallucinogens, and inhalants; and the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives in the civilian, non-institutionalized population of the United States age 12 or older. The survey interviews approximately 67,500 persons each year. The NSDUH provides yearly national and state level estimates of drug abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year and past year abuse or dependence. Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies, Results from the 2007 National Survey on Drug Use and Health: National Findings (2008).

[26] "Lifetime prevalence" is a cumulative indicator of the total number of people who have ever tried drugs, including many in the distant past.

times the number of persons who have used meprobamate products for a non-medical purpose.

Moreover, many reports of carisoprodol abuse have been published both in the United States and in other countries. These cases include the use of carisoprodol by itself and in combination with other drugs of abuse. See also infra Factor 5.

Table Seven: NSDUH Data on Nonmedical Use of Specific Tranquilizer in Lifetime; Numbers in Thousands and Percentage

DRUGS	2004	2005	2006	2007
	# (%)	# (%)	# (%)	# (%)
Benzodiazepines	18,643 (7.8)	19,686 (8.1)	19,662(8.0)	18,934 (7.6)
Valium or Diazepam	14,607(6.1)	14,914 (6.1)	14,824[b] (6[b])	13,172 (5.3)
Meprobamate Products[1]	245 (0.1)	305 (0.1)	216 (0.1)	236 (0.1)
Muscle Relaxants [2]	3,907 (1.6)	3,773 (1.6)	4,449 (1.8)	4,274 (1.7)
Soma®	2,616 (1.1)	2,525 (1.0)	2,840 (1.2)	2,709 (1.1)
Flexeril®	1,968 (0.8)	1,891 (0.8)	2,405 (1.0)	2,438 (1.0)

[1]Includes Equanil®, meprobamate, and Miltown ®, [2] Includes Flexeril® and Soma®, [b]difference between 2006 and 2007 estimates statistically significant, p.≤0.01. Source: SAMHSA, office of Applied Studies, National Survey on Drug Use and Health.

Mr. Dasgupta acknowledged that "NSDUH is a validated and generally scientifically defensible survey." MX 173, at 28. However, he then criticized the study because it relies on self-reporting and because the study does not specifically ask whether carisoprodol or Soma have been used in the "past year" or "past 30 days," although a survey participant may "spontaneously offer[]" that he/she has used the drug within the respective time frame. Id. Mr. Dasgupta further noted that the NSDUH data show that the level of lifetime nonmedical use "is essentially flat

over time and not increasing." Id. at 29.

Nonetheless, that the NSDUH survey has consistently shown that between 2.5 million and 2.8 million persons have engaged in non-medical use of carisoprodol is not evidence of "isolated or occasional nontherapeutic" use. S. Rep. 91-613; reprinted in 1970 U.S.C.C.A.N., at 4602. Rather, it is substantial evidence of "significant use by individuals contrary to professional advice." Id. Where, as here, a drug has been this widely abused, DEA is not required to develop evidence that the rate of abuse is increasing in order to control it.

4. Carisoprodol's pharmacological activities are similar to other drugs with known abuse liabilities.

According to the FDA, when originally marketed in 1959, carisoprodol was described as having qualitatively different kinds of central muscle relaxant properties than meprobamate, a schedule IV depressant (FDA Reference 1).[27] However, the specific mechanisms of action of carisoprodol are not completely understood (2, 3).

FDA found that although carisoprodol is classified as a muscle relaxant, it has little direct effect on skeletal muscle. GX 6, at 5. According to FDA, both carisoprodol and meprobamate possess sedative properties and their therapeutic utility in acute painful musculoskeletal problems may be in part due to these sedative properties. Id. FDA also found that the drugs may be abused for their sedative properties and that in vitro studies demonstrate that carisoprodol elicits barbiturate-like effects. Id; See also discussion infra under Factor Two.

Recent clinical reports addressing carisoprodol's abuse potential and its metabolic conversion to meprobamate have been published in scientific and medical journals. According to FDA, it was initially believed that carisoprodol's abuse potential was primarily related to its metabolic conversion to meprobamate. Id. at 6. However, new animal data from NIDA

[27] The complete list of FDA References 1-58 is attached as Appendix B.

demonstrate that the abuse potential and pharmacology of carisoprodol may be independent of the metabolic pathway in humans to meprobamate. More specifically, FDA cited NIDA studies by Gatch, et al., which show that carisoprodol can be easily recognized by animals in drug discrimination studies as Schedule II, III or IV CNS depressants. (4-6). These studies are discussed more fully below under Factors Two (Scientific Evidence of the Drug's Pharmacological Effect) and Seven (Psychic or Physiological Dependence Potential).

Factor 2 – The Scientific Evidence of Carisoprodol's Pharmacological Effect

Carisoprodol is a centrally-acting muscle relaxant used medically for relief of discomfort associated with acute, painful musculoskeletal conditions, including spasms and spasticity. GX 6, at 6. The original approved therapeutic dose of carisoprodol was 350 mg three times a day, and at bedtime. Id. In placebo-controlled studies, carisoprodol was found more effective than placebo in treatment of acute musculoskeletal disorders (7) and less effective or not different from placebo in chronic disorders. In 2007, FDA approved a 250 mg tablet to be taken three times a day and at bedtime, for up to three weeks. GX 6, at 6.

Although the exact mechanism of muscle relaxant action of this group of drugs is not known, it is believed to occur by depressing interneuronal cells and diminishing the facilitatory background activity on spinal motor neurons and by also inhibiting supraspinal influences, primarily in the lateral reticular area of the brain stem. Id. The polysynaptic reflexes are more readily depressed than monosynaptic reflexes. Id. These drugs produce sedation and drowsiness as their common side effects, which may reflect depressed neuronal activity essential for wakefulness, in the medial reticular ascending system. Id. Despite chemical structures that are unrelated, all muscle relaxants possess sedative properties. Id. The drugs also exhibit anticonvulsant activity in several animal models (3).

Receptor Binding Studies

According to FDA, the complete binding profile of carisoprodol has not been characterized. One study showed that carisoprodol has negligible affinity for the benzodiazepine site, using [^{3}H]-diazepam as a ligand in rat brain tissue (8).

In Vitro Studies

The FDA concluded that the findings of in vitro studies demonstrate that carisoprodol elicits barbiturate-like effects. Whole-cell patch clamp studies were conducted to examine mechanistic similarities between carisoprodol and barbiturates (Schedules II, III or IV, depending on the particular barbiturate) using recombinant rat $\alpha1\beta2$ $GABA_AR$. GX 6, at 6. GABA-gated currents were potentiated by micromolar carisoprodol (EC_{50} = 89 μM)). Id. At millimolar concentrations, currents began to be inhibited, and rebound currents were apparent upon termination of drug administration. Id.

According to FDA, this barbiturate-like trend was consistent with a previous description of carisoprodol effects on human $\alpha1\beta2_y2$ $GABA_AR$ function, demonstrating that carisoprodol, like barbiturates, does not require the y subunit for its activity. Id. at 6-7. Carisoprodol directly activated human $\alpha1\beta2_y2$ $GABA_AR$, producing inward currents in a concentration-dependent manner (EC_{50} = 410 μM). Id. The amplitude of carisoprodol mediated currents (EC_{40}) was reduced to 24 percent of control following incubation with bemegride (a barbiturate antagonist that has not been demonstrated to be specific for barbiturates). Id. By contrast, the benzodiazepine antagonist, flumazenil, had no significant effect on either the allosteric or direct effects of carisoprodol (9).

MEDA challenged the FDA's reliance on this study. More specifically, MEDA elicited the testimony of Dr. Donald Robert Jasinski, who is a Professor of Medicine at the Johns

Hopkins University School of Medicine and the Chief of the Center for Chemical Dependence, Johns Hopkins Bayview Medical Center. MX 172, at 1. Dr. Jasinski testified that even assuming that the model used in this study was "sufficiently robust to establish an affinity of carisoprodol at a GABAα receptor, this does not establish that carisoprodol has barbiturate-like activity, but merely that it, like many other drugs including other non-controlled CNS depressants, has an affinity to attach to a GABAα receptor[]." Id. at 3. Dr. Jasinski then explained that "while barbiturates as a class have an affinity for GABAα receptors, not all drugs that have affinity for GABAα receptors have barbiturate-like activity and/or abuse liability profiles similar to the barbiturates."[28] Id. at 4. Dr. Jasinski further opined that the finding that "bemegride, a non-specific barbiturate antagonist, apparently reduced the amplit[ude] of carisoprodol-mediated currents by 24% [does not] indicate that carisoprodol will have barbiturate like effects." Id.

While Dr. Jasinski may be correct that the findings of the aforementioned study do not conclusively establish that carisoprodol has barbiturate-like effects, there is substantial other evidence in the record (including human studies) which supports this finding. See discussion under Factor Five.

Animal Pharmacology Studies

Berger, et al. (1, 10), described the muscle relaxant and analgesic properties of carisoprodol in animals. Reversible paralysis of voluntary muscles that lasts for nearly 15 minutes occurs in most mice administered carisoprodol (180 mg/kg, i.p.). Paralysis was preceded by signs of excitement manifested by aimless running and staggering, hyperextension

[28] Dr. Jasinski further testified that in a subsequent article, the authors of this study wrote that "[a]lthough both our in vivo and in vitro studies are consistent with barbiturate-like effects of carisoprodol, we are not concluding that carisoprodol is acting at the barbiturate site of the receptor." MX 172, at 3 n.1.

of the neck, and clonic movement of extremities. After administration of high doses, pre-narcotic excitement was absent. During paralysis, respiration and heartbeat were regular, skeletal muscles were relaxed, tremors and twitchings were absent, and corneal reflex was present. Stimulation of the sciatic nerve during paralysis produced prompt muscular response of the leg, indicating that the peripheral nerve, myoneural junction, and muscle were not significantly affected by the drug. Depression of motor activity, as measured by loss of the righting reflex, occurred in 50 percent of animals after oral administration of 400 mg/kg of carisoprodol in mice and 750 mg/kg in rats.

According to FDA, carisoprodol is a relatively poor strychnine antagonist in mice, which differs from other muscle relaxants such as mephenesin (a centrally-acting muscle relaxant that is not marketed in the United States). Carisoprodol depresses the electro-cortical activation response to electrical stimulation of the sciatic nerve, the midbrain reticular formation or of the diffuse thalamic system (nucleus centralis lateralis). Carisoprodol showed an antinociceptive action in response to injection of silver nitrate into joints of rats. Carisoprodol differs from meprobamate (Schedule IV) by not affecting the hippocampal seizures produced by stimulation of the fornix (10).

More recently, the National Toxicology Program of the National Institutes of Environmental Health Sciences examined the toxicity of carisoprodol (11). Male rodents in the 200 mg/kg carisoprodol group and female rodents in the 100 and 800 mg/kg carisoprodol groups had significantly greater mean body weight gains than animals that received vehicle (control group). The incidence of adverse events was dose-related, and females were more sensitive than males to the effects of carisoprodol. Carisoprodol induced ataxia and prostration in rats and mice, increases in liver weights in rats and mice, and nephropathy in male rats.

In cats, carisoprodol was very effective in abolishing decerebrate rigidity, whereas meprobamate and mephenesin had no effect on spasticity. Carisoprodol appeared to be eight times more potent than these drugs in alleviating decerebrate spasticity (l0).

In dogs, carisoprodol (100 mg/kg p.o.) produced loss of muscle tone. At larger doses (200 mg/kg p.o.), signs of excitement characterized by tail wagging and howling were observed along with muscular weakness and ataxia with no tremors, convulsions or salivation (10).

Self-Administration Studies

The FDA found that carisoprodol has positive reinforcing effects, in that rhesus monkeys maintained self administration responding that was greater than rates maintained by saline, although less than rates maintained by i.v. injections of methohexital (C-IV). GX 6, at 8. However, because of the limited solubility of carisoprodol, doses larger than 0.3 mg/kg injection could not be tested. NIDA Research Monograph, volume 146:423-433 (1999). This dose (0.3 mg/kg/injection) is lower than the doses used orally in humans. GX 6, at 8.

Drug-Discrimination Studies

According to the FDA, "drug discrimination studies in animals are believed to be predictive of subjective effects in humans and are thus useful in assessing the abuse potential of drugs." Id. Carisoprodol can stimulate the barbiturate site on the GABA-A receptor. In drug discrimination studies, pentobarbital (C-II) fully substitutes in carisoprodol-trained rats and bemegride fully antagonizes the subjective effects of carisoprodol.

FDA also noted that another study found that in dogs tolerant and dependent on barbital (C-IV), oral doses of 200 mg/kg of carisoprodol every six hours were completely effective and

equivalent to 100 mg/kg of barbital in preventing the appearance of abstinence phenomena (12).

Bemegride fully blocked the discriminative stimulus effects of the training dose of carisoprodol (100 mg/kg p.o.), whereas the benzodiazepine antagonist, flumazenil, produced a moderate attenuation of the discriminative stimulus effects of carisoprodol across a wide range of doses. According to FDA, these findings suggest that carisoprodol may directly activate or allosterically modulate $GABA_A$ receptors which mediate the discriminative stimulus effects of carisoprodol. FDA further found that the actions of carisoprodol at the barbiturate site may be more relevant than actions at the benzodiazepine site and that certain effects of carisoprodol may be independent of its metabolism to meprobamate (C-IV) (9).

Gatch, et al., (4) assessed the ability of rats to discriminate carisoprodol from vehicle. Rats were trained to discriminate carisoprodol and a carisoprodol dose-effect curve was established for doses from 25 to 100 mg/kg. Meprobamate (C-IV), pentobarbital (C-II/ C-III), and chlordiazepoxide (C-IV) were each tested for their ability to substitute for the discriminative stimulus effects of carisoprodol; each was found to substitute fully for the discriminative stimulus effects produced by 100 mg/kg of carisoprodol.

In another study, Gatch, et al. (5), found that 5 mg/kg bemegride antagonized the discriminative stimulus effects produced by 100 mg/kg of carisoprodol in rats trained to discriminate carisoprodol and decreased the response rate to 79 percent of the carisoprodol control group. Gatch, et al. (6), also studied the effects of carisoprodol in the presence of Cimetidine, to determine if the effects of carisoprodol are produced by its active metabolite, meprobamate. Cimetidine, a P450 enzyme inhibitor, which prevents the conversion of carisoprodol to meprobamate, failed to inhibit the discriminative stimulus effects produced by 100 mg/kg of carisoprodol in rats trained to discriminate carisoprodol. According to FDA, these

results suggest that carisoprodol can produce discriminative stimulus effects directly without being converted into meprobamate.

Dr. Jasinski disputed the FDA's reliance on the various animal studies it used to assess carisoprodol's abuse potential. MX 172, at 4-7. While Dr. Jasinski acknowledged that "in these studies the animals reflected behavior patterns with respect to carisoprodol that suggest patterns similar to barbiturates," he then opined that "due to the inherent limitations of animal studies they simply do not provide an adequate basis to make decisions concerning abuse potential in humans." Id. at 4. Dr. Jasinski offered no further explanation as to what those limitations are. Moreover, at the hearing, Dr. Jasinski testified that it is appropriate to rely on animal studies as one aspect of assessing a drug's abuse potential in humans.[29] Tr. 721.

With respect to the self-administration study involving rhesus monkeys, Dr. Jasinski explained that the fact that "the monkeys seem[ed] to prefer carisoprodol over a saline, but less than a schedule IV substance, merely indicates that the . . . monkey prefers carisoprodol over saline" and that "[t]his preference could be due to factors unrelated to any potential for abuse in humans." Id. at 5.

As for the drug-discrimination studies involving rats, Dr. Jasinski acknowledged that the study showed that "pentobarbital substitutes for carisoprodol in rats trained to discriminate carisoprodol and that" bemegride, a barbiturate antagonist, "blocked the discriminate stimulus effects." Id. Dr. Jasinski then opined that "these data at most are only indicative that carisoprodol may have certain effects similar to those of barbiturates (e.g., they have activity at the GABA receptor site) and not that any such similarity translates into a similar potential abuse

[29] In its brief, Meda argues that animal studies "are significantly less probative than human studies" in assessing a drug's abuse potential. Meda Br. 25. However, Meda did not establish the degree to which animal studies are less probative than human studies and even its Expert conceded that it is appropriate to rely on animal studies in assessing abuse potential in humans. Tr. 721. While Meda cites human data – in particular, the results of recent clinic trials it conducted and the Fraser study - and argues that this data should be given greater weight than the animal studies, as discussed below, both studies have significant limitations.

liability." Id. Dr. Jasinski further explained that "it is well known that certain drugs will substitute for drugs of abuse without themselves being subject to any significant drug abuse." Id.

As for the study showing that 200 mg/kg of carisoprodol substituted for 100 mg/kg in dogs which are dependent on barbital, Dr. Jasinski noted that the authors had concluded that carisoprodol was an exception to the general rule that "whenever drugs produce physiological dependence in which abstinence syndrome is similar, these drugs must possess a common mechanism of action and abuse liability profiles." Id. at 6 (citing MX 91). As Dr. Jasinski observed, based on several unpublished studies which showed that "the chronic administration of carisoprodol in 4 divided doses of 1 gm/day for 6 months [did] not result in the development of physiological dependence," the authors concluded that "[t]he fact that carisoprodol did effectively substitute for sodium barbital in [their] study indicates that false positive results are possible from the substitution evaluation of barbiturate-like physiological dependence capacity." MX 91; see also MX 172, at 6.

However, as the authors made clear, their conclusion that carisoprodol produced a false positive was based on studies which showed that taking one gram per day of the drug did not cause physiological dependence. Thus, this study does not foreclose the possibility that chronic use of carisoprodol in daily doses of greater than one gram per day could cause physiological dependence and calls into question the validity of the authors' conclusion that carisoprodol caused a false positive when substituted for barbital.

Accordingly, even discounting the rhesus monkey study, I find that substantial evidence supports the FDA's conclusion that the drug-discrimination studies in both dogs and rats indicate that carisoprodol has positive reinforcing and discriminative effects similar to other drugs currently regulated under C-IV, including barbital, meprobamate, and chlordiazepoxide.

Clinical Experience and Human Studies

Pharmacodynamic Effects

Beebe, et al. (13), reviewed the pharmacodynamic effects of carisoprodol. Lethargy, drowsiness, ataxia, dysmetria and fatigue are common side effects at therapeutic doses[30] and in overdose (14). More severe CNS-related effects including confusion, amnesia and coma occur less frequently at therapeutic doses, but occur with overdose (15; 16). Respiratory depression may occur in patients with significant CNS depression (17; 18).

The primary toxic effect with poisoning or exposure to carisoprodol is CNS depression and, in severe cases, coma. Euphoria, CNS stimulation, muscular incoordination, confusion, headache, hallucinations and dystonic reactions have also been reported. Anti-cholinergic effects (tachycardia, dry, warm skin) are reported following carisoprodol poisoning. Fever is reported following carisoprodol overdose (14; 19). Both mild hypertension and mild hypotension are reported in conjunction with serotonin syndrome after carisoprodol overdose (19). Horizontal nystagmus, mydriasis, and blurred vision have also been reported with carisoprodol overdose (20).

In addition to the above adverse effects, drug abuse, dependence and tolerance are reported following long-term use of carisoprodol. See infra Factor Seven.

Human Behavioral Studies.

Fraser, et al. (21), evaluated whether carisoprodol possessed morphine-like (C-II) or barbiturate like (C-II, C-III and C-IV) addictive properties in human subjects, all of whom "were former opiate addicts." H.F. Fraser, et al., Evaluation of carisoprodol and phenyramidol for addictiveness, Bulletin on Narcotics 1 (Oct-Dec. 1961). The study had three arms: the first

[30] See current label information for carisoprodol (Soma) (http://www.fda~gov/cder/foil1abe1l2007 /0 11792s0411bl.pdf).

evaluated the effect of single oral doses in non-addicted patients, the second evaluated the 24-hour substitution of carisoprodol for morphine in morphine-stabilized patients and was used to assess whether carisoprodol can prevent symptoms of abstinence from morphine, and the third assessed physical dependence following chronic administration of carisoprodol and abrupt discontinuation of the drug. See id.

In the first arm of the study, single doses of carisoprodol ranging from 1,050 mg to 2,500 mg (three to seven times the usual dose of 350 mg) were administered orally in capsules to fasting, non-tolerant opiate addicts. Id. Assessments were carried out hourly for six hours with the single-dose opiate questionnaire. Id.

The study found that carisoprodol's effects were not consistent at doses lower than 2,000 mg. Id. at 1-2. Only one of fifteen subjects that received the 2,500 mg dose identified the drug as "dope." Id. In the same dose-range group, most subjects became sleepy one or two hours after receiving 2,500 mg of carisoprodol, and when awakened, did not show as much dysarthria as would have been anticipated from an equivalent dose of barbiturates. Id. at 2. According to the FDA, the subjective and objective effects noted in this group were similar to those of barbiturates or alcohol and different from those of opiates. GX 6, at 10.

In the second arm of the study, 3,600 to 4,800 mg of carisoprodol, which was divided into three equal oral doses, were substituted for morphine in six and three morphine-stabilized patients, respectively. Fraser, at 2. The study was controlled "negatively, by substitution of a placebo for morphine, and positively, by continuing the customary dose morphine in the same subjects." Id. Moreover, because "carisoprodol seemed to be barbiturate-like in many respects, the study was also controlled by substituting" an average dose of 1.11 g of pentobarbital for morphine, which was divided among five doses, in another experiment which involved eleven

other subjects. Id. Following substitution, hourly "[o]bservations for the intensity of abstinence were made . . . from the 11th through the 24th hour of abstinence." Id.

This arm of the study concluded that "carisoprodol partially but significantly suppressed symptoms of abstinence." Id. The study found that the patients receiving the 4,800 mg dose of carisoprodol "were quite sedated and somewhat difficult to arouse, but showed only a slight degree of dysarthria and ataxia." Id.

The FDA did not discuss the third arm of the study. See GX 6, at 10. Instead, it concluded that this study was conducted before the advent of modem human abuse liability testing that uses validated measures, and that it therefore does not directly address the issue of the human abuse potential of carisoprodol. Id. However, the FDA further found that "the study results indicate that carisoprodol has sedative-like effects, as opposed to opiate-like effects." Id.

Dr. Jasinski expressed his disagreement with the FDA's assessment of the validity of the study results, opining that "[w]hile there have been enhancements in methodologies use[d] to assess abuse liability in intervening years, . . . the methodology used by Fraser yielded valid scientific results and should not be discounted based solely upon the fact that different methodologies would be used today." MX 172, at 7. Dr. Jasinski found it "significant that in the Fraser study[,] the chronic administration of carisoprodol for a period of 18 to 54 days at doses that progressed from 1200 mg/day to 4800 mg/day . . . did not induce a characteristic barbiturate intoxication pattern," and that "the abrupt withdrawal of carisoprodol [did not] reveal any signs of barbiturate-like abstinence." Id. at 7-8. Dr. Jasinski thus opined that "these data show that carisoprodol does not possess barbiturate-like abuse liability and that in light of these data[,] it is not scientifically sound to reach a contrary conclusion based solely upon less reliable

animal or in vitro data." Id. at 8.

Both parties and the ALJ cited the Fraser study as being an exhibit in the record. See Gov. Br. at 19 (citing Meda Ex. 98); Meda Br. at 56-57 (citing same), ALJ at 32 (¶ 46). However, this exhibit was not included in the record forwarded to this office, and a review of the transcripts contains no indication that Meda Exhibit 98 was ever entered into evidence. Because both parties and the ALJ have cited the Fraser study as if it were in evidence, I take official notice of it. Moreover, given the dispute as to significance of the study's findings, a discussion of the third arm is warranted.

The third arm of the Fraser study, which was only single-blinded,[31] involved the administration of large doses of carisoprodol to five patients, with four of the patients receiving the drug for 18 days and one receiving the drug for 54 days. Fraser, at 3. Each patient received an initial dose of 1,200 mg, which was increased by 200 mg each day for 16 days, and then by 300 mg on days 17 and 18 for a maximum daily dose of 4800 mg. Id. The patient who was given the drug for 54 days received a daily dose of 4800 mg from days 18 through 54. Id. Following the respective 18 and 54-day periods, the drug was abruptly withdrawn from the patients, who were then given placebo. Id.

The study found that with the exception of changes in the patients' EEG (electroencephalogram) patterns, "the outstanding feature was a complete absence of any significant subjective effects even when the dosage was increased to 4,800 mg daily." Id. Continuing, the authors noted that "it was not possible to differentiate carisoprodol from a placebo." Id. Moreover, following the cessation of carisoprodol, none of the patients showed signs of abstinence and all were unaware that their medication had been changed. Id.

[31] While the patients "were unaware of the nature and schedule of medication," the observers were not. Fraser, at 3.

While the study found that the patients' EEGs showed a "barbiturate-like effect" when the patients were receiving 4200 to 4800 mg, it also found that all of the patients' EEGs had returned to normal within thirty-six hours of the last dose. Id. Moreover, "[n]one of these patients showed focal or generalized abnormalities of the paroxysmal type during withdrawal, such as those seen following withdrawal of barbiturates." Id. The study thus concluded that "[c]hronic administration on a progressive dosage schedule did not induce a characteristic barbiturate intoxication pattern" and that the abrupt withdrawal of the drug did not result in "barbiturate-like abstinence" symptom. Id.

However, the authors noted that "it remains to be seen whether administering carisoprodol continuously in larger doses would induce a chronic state of intoxication and whether abrupt withdrawal under such circumstance would provoke a barbiturate or meprobamate type of abstinence." Id. The authors further noted that "[s]uch a possibility is suggested by the fact that carisoprodol is a congener of meprobamate and exhibits many barbiturate-like pharmacological effects." Id. at 3-4.

As for Dr. Jasinski's testimony that the Fraser study "yielded valid scientific results," another of Meda's Exhibits (the FDA's Draft Guidance on Assessment of Abuse Potential of Drugs) states that "[h]uman abuse potential studies are usually double blind, double dummy, placebo, and positive comparator controlled, and are crossover designed." MX 12, at 14. Moreover, such studies typically involve a substantially greater number of patients than the Fraser study involved and both "[t]he investigator and the staff who interact with subjects should not know the sequence of substances administered." Id. In short, the Fraser study did not meet most of these criteria. Moreover, it seems unlikely that scientists would draw a definitive

conclusion from the findings with respect to the single patient who received the drug for 54 days.

Meda also cites recent clinical trials it conducted in support of its application to market carisoprodol in 250 mg strength as evidence that the drug does not cause withdrawal symptoms and is not subject to diversion, misuse, or abuse. MX 171, at 5. MEDA's CMO maintains that these studies, which involved several thousand patients at hundreds of clinical research centers, "provide the only evidence-based body of human data from which [to] evaluate the likelihood of drug diversion, drug seeking behavior, and withdrawal symptoms in a controlled setting." Id. at 9 (emphasis in original). According to MEDA's CMO, during these studies, there was no evidence of diversion and "there was no evidence whatsoever of carisoprodol-induced withdrawal syndrome following abrupt cessation of up to two weeks of treatment." Id. at 10. Meda's CMO then opined that "[u]nlike other drugs, such as opioids, this suggests that if dependence occurs, it is only following prolonged treatment with carisoprodol." Id.

As for the lack of evidence of withdrawal, diversion or drug seeking behavior, the short-term nature of the studies (which involved administration of the drug at therapeutic levels for either one or two weeks at most, MX 171, at 8) renders this evidence of minimal value in determining whether carisoprodol causes dependency. Moreover, FDA found that there is extensive evidence in the scientific literature establishing that carisoprodol can cause dependency in humans. See discussion under Factors Five, Six, and Seven, infra. Finally, that short-term administration of carisoprodol does not cause dependency is not dispositive because the CSA does not impose an arbitrary time frame for assessing whether the taking of a drug can cause dependency.[32]

[32] Dr. Jasinski also noted that in his experience as the Chief of the Center for Chemical Dependence at Johns Hopkins Bayview Medical Center, he could not "recall a single incidence in which an individual has visited our center to be treated for carisoprodol addiction/dependence." MX 172, at 9. While that may be, this may simply reflect that different drugs are more popular with drug abusers in the geographic area served by Johns Hopkins.

Factor 3 - The State of Current Scientific Knowledge Regarding Carisoprodol

The current scientific knowledge regarding carisoprodol includes information about the drug's chemistry and pharmacokinetics.

Chemistry

Chemically, Carisoprodol is (l-methylethyl) carbamic acid 2-[[(aminocarbonyl)oxy]methyl]-2- methylpentyl ester; N-isopropyl-2-methyl-2-propyl-l ,3-propanediol dicarbamate; isopropyl meprobamate. GX 6, at 10. Carisoprodol is also identified by CAS number 78-44-4. Carisoprodol has a molecular weight of 260.33; its molecular formula is $C_{12}H_{24}N_20_4$. Id.

Carisoprodol is a bitter tasting, odorless, white crystalline powder. Its melting point (without decomposition) ranges from 92-94°C and it has low water solubility (30 mg/l00 ml at 25°C). Id. Carisoprodol is soluble in many organic solvents and practically insoluble in vegetable oils. Id. Carisoprodol is stable in dilute acid and alkali and is not altered by artificial gastric or intestinal juices. Id. It is a racemic compound with one asymmetric center. Id. Qualitative and quantitative methods for detection of carisoprodol and other drugs by gas chromatography/mass spectrometry (GC/MS) or thin layer chromatography in combination with GC/MS have been published (22-25).

Pharmacokinetics

The pharmacokinetics of carisoprodol have been investigated in several animal and human studies. At a dose of 350 mg, the mean peak plasma concentration (Cmax) achieved was

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Dr. Jasinski also noted that according to the Treatment Episode Data Set, a database maintained by SAMHSA of admissions to substance abuse treatment centers, "there were no mentions of carisoprodol in any of the TEDS reports from 2002 through 2007." Id. (citing MXs 31 & 32). However, the TEDS reports do not separately list carisoprodol, but rather use broader categories such as "Other non-Benzodiazepine Tranquilizers," which "[i]ncludes meprobamate, tranquilizers, etc." MX 31, at 28. Thus, admissions to treatment centers for carisoprodol abuse might well be reported under this category. Accordingly, I place no weight on this testimony.

2.29 ± 0.68 μg/ml; women tended to reach peak plasma concentrations earlier than men (1.45 vs. 2.5 hrs) and had a faster apparent oral clearance (0.772 vs. 0.38 l/h/kg). GX 6, at 10. Carisoprodol is metabolized in the liver via cytochrome 2D6. Id. Meprobamate (C-IV) is one of the products of carisoprodol metabolism. Id. Following a single 350 mg dose of carisoprodol, the corresponding normalized peak concentration of meprobamate was 2.08 ± 0.48 μg/ml; these levels are approximately 25 percent those observed following a single 400 mg dose of meprobamate. Id. Carisoprodol is eliminated by both renal and non-renal routes with a terminal elimination halflife of 2.44 ± 0.93 hr. Id. at 10-11.

Factor 4 – Carisoprodol's History and Current Pattern of Abuse

In 1959, carisoprodol was introduced into the U.S. market as a single-agent drug, and in 1960, as a combination product with aspirin. Id. at 11. In 1983, carisoprodol was marketed in combination with aspirin and codeine. Id. Numerous generic products have been introduced into the U.S. market. Id. Carisoprodol is also marketed worldwide under various trade names including Artifar, Carisoma, Carisoprodol Sintesina, Listaflex, Mio Relax, Sanoma, Soma, Somadril, and Somflam. Id.

In assessing carisoprodol's history and current pattern of abuse, DEA and FDA relied on multiple data sources. As discussed above, these include DAWN, NSDUH, AERS, and Florida Medical Examiners Commission Data. In addition, reports from the scientific literature were reviewed.

DAWN ED Data

As discussed above under Factor One (and as set forth in Table One), DAWN data suggest that there has been an increase in the frequency of nonmedical use ED visits associated

with carisoprodol. In 2004, DAWN estimated the number of ED visits related to nonmedical use of carisoprodol as 14,736; in 2007, it estimated that there were 27,128 nonmedical ED visits related to carisoprodol. By comparison, DAWN estimated that in 2004, there were 15,619 ED visits related to the nonmedical use of diazepam, and in 2007, there were an estimated total of 19,674 nonmedical ED visits related to diazepam. However, according to SAMHSA, the increase in the number of carisoprodol visits between 2004 and 2007 was not statistically significant. Nonetheless, even if there were only an estimated 14,736 ED visits related to carisoprodol, this is still a significant number of visits when compared with the number of diazepam-related visits.

In addition, as found above under Factor One (and set forth in Table 2), when the number of estimated nonmedical use ED visits is adjusted for the number of prescriptions issued (by dividing the number of visits by 10,000 prescriptions), in 2007 the carisoprodol rate was 22.6/10,000 Rx, while diazepam's rate was 14.1/10,000 Rx. By contrast, cyclobenzaprine, another skeletal muscle relaxant, had a rate of 3.3/10,000 Rx.

As also found above under Factor One, NSDUH survey data for the years 2004 through 2007 show that between 2.5 and 2.84 million persons have used carisoprodol for non-medical purposes. To be sure, the NSDUH data may not reflect a statistically significant increase in the number of persons who have used carisoprodol for a non-medical purpose. However, the fact that approximately 2.5 to 2.8 million persons have engaged in non-medical use of carisoprodol is itself significant.

Demographic and epidemiological factors associated with nonmedical use of carisoprodol

FDA's review found that the majority of cases reported in the scientific literature note

that carisoprodol abuse has primarily been a component of multi-drug abuse. GX 6, at 13. According to FDA, DAWN data indicates that the drugs most frequently used in combination with carisoprodol that resulted in ED visits were opioids (hydrocodone, oxycodone), benzodiazepines (alprazolam, diazepam, clonazepam), alcohol, and illicit drugs (marijuana, cocaine). Id. at 14.

Beginning in 2006, carisoprodol has been reported as a primary or sole drug of abuse in DAWN. Additional analysis of DAWN data specifically addresses details of this issue for carisoprodol nonmedical use in 2006 (see Table 3).

As set forth in Table 3, the DAWN 2006 data estimated that there were a total of 24,505 ED visits related to the nonmedical use of carisoprodol. Of these, 42 percent involved females and 58 percent males. In twenty-one percent of the cases, carisoprodol was reported as the sole drug, with it being the sole drug in twenty-seven percent of the female cases, and twelve percent of the male cases. The FDA's analysis concluded that these gender-based differences may suggest effects related to dosage and pharmacokinetic/pharmacodynamic effects that could influence abuse potential.

The DAWN data also suggest that there are some age-related differences in the use of carisoprodol, with greater reports of single use among those 12-17 years old (27 percent) and those 45 – 54 years old (30 percent) than other age groups.[33] A study by Forrester (26) found that adolescents accounted for 17 percent of the abuse calls related to carisoprodol in an analysis

[33] According to FDA, "such abuse may represent a significant change in the pattern of abuse of carisoprodol, as abuse of carisoprodol without other substances and significant single drug use by such a large young population has not previously been documented in national data." GX 6, at 14. However, prior to 2006, carisoprodol was not previously reported as a sole drug in the DAWN ED data. Thus, it is unclear whether there has been a significant change in the abuse of carisoprodol by adolescents.

of Texas Poison Centers' data from 1998 - 2003, a rate similar to that reported in RADARS (27).

Table 8: Estimated Nonmedical-Use Carisoprodol ED Visits from DAWN 2006 by Age and Most Common Drug Combinations[34]

		AGE										
Carisoprodol	All	0-5	6-11	12-17	18-20	21-24	25-29	30-34	35-44	45-54	55-64	65+
Carisoprodol-single drug	5,053			307	256	553	494	287	1,030	1,873	228	26
Carisoprodol-multi-drug	19,444	0	...	820	1,135	2,342	2,318	2,150	5,119	4,286	752	515
Total by Age	24,497	0	...	1,127	1,391	2,895	2,812	2,437	6,149	6,159	980	541

NSDUH data for the years 2004 through 2007 show that in each year, more than 100,000 twelve to seventeen-year olds reported having used carisoprodol for non-medical reasons. During this same timeframe, between 956,000 and 1,056,000 eighteen to twenty-five year olds reported having used carisoprodol for non-medical reasons. As the table below shows, these age groups reported having engaged in the non-medical use of carisoprodol to a far greater extent than they report having engaged in the non-medical use of meprobamate.[35] These figures were approximately thirty-three percent (in the 12-17 age group) and forty-two percent (in the 18-25 age group) of those persons reporting non-medical use of diazepam.

[34] Where age was known. Information received from SAMHSA on June 18, 2008. Three dots (...) indicate that an estimate or count of less than 30 or with a relative standard error greater than 50, has been suppressed.

[35] Nearly twice as many persons reported non-medical use of carisoprodol than reported non-medical use of cyclobenzaprine, another muscle relaxant which is unscheduled. GX 6, at 17.

Table 9: NSDUH - Nonmedical Use of Carisoprodol (Soma®) and Other Drugs in Lifetime, by Age Group: Numbers in Thousands (%), 2004 -2007

Age Groups	2004	2005	2006	2007
	#(%)	#(%)	#(%)	#(%)
Carisoprodol (Soma®)				
Ages 12-17	138 (0.5)	118 (0.5)	111(0.4)	106 (0.4)
Ages 18-25	975 (3.0)	1,056 (3.3)	1,034 (3.2)	956 (2.9)
Ages 26 or Older	1,503 (0.8)	1,351 (0.7)	1,695 (0.9)	1,647 (0.9)
Cyclobenzaprine (Flexeril®)				
Ages 12-17	34[a](0.1[a])	64 (0.3)	53 (0.2)	56 (0.2)
Ages 18-25	461 (1.4)	479 (1.5)	533 (1.6)	568 (1.7)
Ages 26 or Older	1,473 (0.8)	1,348 (0.7)	1,819 (1.0)	1,813 (1.0)
Diazepam (Valium®)				
Ages 12-17	380 (l.5)	351 (1.4)	320 (1.3)	314 (1.2)
Ages 18-25	2,434 (7.6)	2,650 (8.2)	2,480[a] (7.6[a])	2,252 (6.9)
Ages 26 or Older	11,794 (6.4)	11,913 (6.4)	12,024[a] (6.4[b])	10,606 (5.6)
Meprobamate Products[1]				
Ages 12-17	34 (0.1)	22 (0.1)	24 (0.1)	18 (0.1)
Ages 18-25	39 (0.1)	49 (0.2)	42 (0.1)	27 (0.1)
Ages 26 or Older	173 (0.1)	234 (0.1)	150 (0.1)	192 (0.1)

As found above, AERS data through June 2007 contains a total of 472 reports related to potential abuse of carisoprodol. GX 6, at 15. Of these, 48 reports identified dependence as the adverse event and 19 identified withdrawal syndrome. Id. As also found above, data obtained from the Florida Medical Examiners Commission for the years 2004 through 2008 identifies carisoprodol as the cause of death in between 74 and 96 deaths each year.[36] See Table Four above.

Scientific Literature Reports

The FDA review concluded that there are relatively few reports in the scientific literature describing fatal cases of intoxication with carisoprodol. The FDA further found that there are inconsistencies in the literature with regard to what is considered a toxic concentration level (17, 22, 28-31). As carisoprodol is frequently abused in combination with other drugs, the specific contribution of carisoprodol to a fatality may be difficult to ascertain. However, several

[l] Includes Equanil® meprobamate, and Miltown® [a] Difference between year and succeeding year (e.g., 2004 and 2005) estimates are statistically significant, p≤0.05. [b] Difference between year and succeeding year statistically significant, p≤0.01. Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health.

publications have attributed therapeutic levels of carisoprodol at 10 - 40 mg/l, toxic levels at 30-50 mg/l, and a lethal level at 110 mg/l (31-33).

Davis and Alexander (31) reviewed carisoprodol-related deaths in Jefferson County, Alabama, from January 1, 1986 to October 31, 1997. Of a total of 8,162 Medical Examiner cases, toxicology analysis found 24 cases in which carisoprodol was in the decedent's blood. Blood carisoprodol concentrations in decedents ranged from <1 mg/l to 96.8 mg/l, with a mean carisoprodol concentration of 16.4 mg/l and a standard deviation of 21.0 mg/l. In no case was

[36] The data for the years 2004 through 2008 show that carisoprodol was present in between 289 and 415 cases each year. GX 6, at 18.

carisoprodol the only drug detected, nor was it ever the sole cause of death. The authors also noted the frequent association in their series and in the DAWN data of carisoprodol with co-ingested respiratory depressants (propoxyphene, diazepam, codeine). As carisoprodol also can cause respiratory depression, the authors concluded that it was a probable contributor to the cause of death (31).

Hoiseth, et al. (34), investigated all forensic autopsies at the Norwegian Institute of Public Health during the period 1992-2003 and found five cases which reported the median concentrations of carisoprodol associated with intoxication. In another 93 intoxication cases, levels of carisoprodol relative to the other drugs varied. When the number of intoxications with carisoprodol each year was divided by the number of defined daily doses (DDD) sold, a fatal toxicity index (FTI) of between 5.6 and 6.9 deaths/million DDD was obtained. The carisoprodol FTI was higher than data for the schedule IV CNS depressants diazepam (5.2), oxazepam (4.9), nitrazepam (2.8), and zopiclone (1.9), but lower than those for alprazolam (16.0) and clonazepam (16.1). The total number of cases involving carisoprodol increased during the time period observed, as did sales figures for the same period. Only a small number of deaths could be attributed to use of carisoprodol alone.

In summary, multiple national and state data systems used in the United States provide substantial evidence that carisoprodol is being abused. This conclusion is corroborated by various reports published in the scientific literature. While carisoprodol is most often abused in combination with other drugs, in about 20 percent of the reports carisoprodol is the only drug of abuse. In addition, national survey data show that in excess of one million people under the age of twenty-six have acknowledged using carisoprodol for non-medical reasons. These data are consistent with DEA data indicating that carisoprodol is being diverted.

Factor 5 - The Scope, Duration, and Significance of Abuse

According to the FDA, examination of the case reports and studies of abuse in the United States and other countries are useful in assessing the scope, duration, and significance of carisoprodol abuse. GX 6, at 19. Because carisoprodol has been marketed since 1959, there is a substantial body of post-marketing epidemiologic abuse-related data in the published scientific literature and from AERS. Id. at 19-20. Drug abuse and dependency are determined by the evaluation of a patient's drug-seeking behavior, as evidenced by the use of multiple prescribers, the increased frequency of refills, the use of increasing doses, and reports of withdrawal symptoms when a drug is suddenly withdrawn. Id. at 20. Withdrawal symptoms vary and include anxiety, tremor, insomnia, hallucinations, and seizures. Id.

Reports in the scientific literature document that carisoprodol can cause dependency (35-39) and there are cases where withdrawal symptoms have been reported (40-42). While the presence of other drugs of abuse complicates the assessment, there are reports where carisoprodol is the sole drug of abuse (35, 43) (see Factor 7 for further details of these reports).

There are other reports in addition to those discussed under Factor Four. A report from India describes sixteen cases of carisoprodol abuse, mainly among young male polydrug abusers (15). Carisoprodol was purportedly taken to attenuate opioid withdrawal, but its abuse for pleasurable effects was also described. Carisoprodol thus gained a reputation among addicts for producing psychic effects. Isaac, et al. (44), reported a case of abuse from Canada that was recognized through a pharmacist hotline.

Bramness, et al. (45), conducted a pharmacoepidemiological study on the use and abuse of carisoprodol in Norway. The study used the Norwegian Prescription Database (NorPD), which contains information on prescription drugs dispensed in Norway. An advantage to this

database is that patients were followed over time. In 2004, 53,889 Norwegian women (2.4 percent) and 29,824 men (1.3 percent), age 18 or older, received carisoprodol at least once. At the time of the study, carisoprodol was approved in Norway for the treatment of acute low back pain, for short term use only (up to 1 week) at a defined daily dose (DDD) of 1400 mg (350 mg three times a day and at bedtime).

The investigation included the dispensing of 3,772,154 DDDs to 83,713 patients of 18 years of age or older. Measured parameters included the one year prevalence of use (i.e., the number of individuals who had received at least one prescription of carisoprodol per 100 inhabitants) and parameters for potential abuse including high use (high users were defined as those receiving >15 DDDs during the year), high intensity use (high intensity over different lengths of time), doctor shopping, and concomitant use of potential drugs of abuse. The possible drug abuse parameters for carisoprodol were compared to five other commonly prescribed drugs.

Of those meeting the study's requirements, the following groups emerged: therapeutic users, 62 percent; pseudo-therapeutic long-term users of carisoprodol, 16 percent; "pure" carisoprodol abusers, 1 percent; concomitant benzodiazepine abusers, 8 percent; and concomitant opioid abusers, 14 percent. The therapeutic users received only 12 percent of the carisoprodol dispensed in 2004, while those considered primary opioid abusers received 48 percent of the total amount of dispensed. Eighty-nine percent of the patients received their carisoprodol from a single prescribing doctor, with the remainder having multiple prescribers. Eighty-two percent of the patients were defined as high users (received $\geq$ 15 DDDs) of carisoprodol and 14 percent of the patients received $\geq$75 DDDs.

Reports in the scientific literature indicate that relatively few physicians are aware of the addictive potential of the drug (39; 46; 47). The lack of medical and public awareness regarding

the abuse potential of carisoprodol may contribute to the abuse of the drug.

In summary, carisoprodol's post-marketing history indicates that the drug can, and is, being abused, in both the United States and other countries. The growing evidence includes epidemiologic abuse-related data in the published scientific literature (e.g., Bramness) and from AERS, as well as data from national and state data systems that track drug abuse. While recent data show that carisoprodol is most commonly abused in combination with other drugs, DAWN data show that it is abused as a single drug in 20 percent of the cases. Other data (the NSDUH survey) show that carisoprodol is being widely abused by adolescents and young adults.

The human data showing abuse are reinforced by recent animal self-administration and drug-discrimination studies indicating that carisoprodol has positive reinforcing and discriminative effects similar to other drugs currently controlled under schedule IV, including barbital, meprobamate, and chlordiazepoxide.

Factor 6 – The Risk to the Public Health

The scientific literature and other data, including DAWN, NSDUH, and AERS, document the adverse health consequences of the use, misuse, and abuse of carisoprodol. According to the FDA, the risks of carisoprodol to the public health are typical of other CNS depressants that are controlled in the CSA. GX 6, at 21. These risks include CNS depression, respiratory failure, cognitive and motor impairment, addiction, dependence, and abuse. Id.

Because carisoprodol metabolizes to meprobamate (C-IV), carisoprodol may pose similar risks to the public health as those exhibited by meprobamate. Olsen, et al. (48), concluded that the meprobamate formed during carisoprodol metabolism may contribute to the effects of carisoprodol. A case report of a pediatric death due to CNS depression and respiratory failure as

a consequence of a carisoprodol overdose indicates that oral ingestion of carisoprodol alone could produce significant serum levels of both carisoprodol and meprobamate (17).

Backer, et al. (22), reported three cases involving overdoses of carisoprodol and measured the concentration of carisoprodol and meprobamate in urine, vitreous humor, heart and femoral blood by GC/MS. In the first case, which involved a 43-year old woman, an empty bottle of 30 tablets of carisoprodol was found next to her. The prescription had been filled 3 days earlier. Only carisoprodol and meprobamate were detected, but the concentrations varied by anatomical site.

Carisoprodol has been implicated in cases of impaired driving (49-52). Logan, et al. (50), reported the analytical results from a Washington State Toxicology Laboratory (WSTL) review of drivers suspected of driving under the influence of drugs and further reviewed the pharmacology of the carisoprodol and meprobamate, including literature implicating these drugs in impaired driving. They found 104 cases submitted to the WSTL between January 1996 and July 1998 in which meprobamate and/or carisoprodol was detected in the blood of drivers involved in accidents or arrested for impaired driving. Analytical toxicology, patterns of drug use, driving behaviors, and symptoms observed in the drivers were considered. The symptomatology and level of driving impairment were consistent with that of other CNS depressants, most notably alcohol. Reported driving behaviors included erratic lane travel, weaving, driving slowly, swerving, stopping in traffic, and hitting parked cars and other stationary objects. Drivers stopped by the police displayed poor balance and coordination, horizontal gaze nystagmus; bloodshot eyes; unsteadiness; slurred speech; slow responses; a tendency to doze off or fall asleep; difficulty standing, walking or exiting their vehicles; and disorientation.

Many of these cases involved drivers who had also taken alcohol or other CNS active drugs, making it difficult to attribute the documented impairment solely to carisoprodol and meprobamate. However, in twenty-one cases, no other drugs were detected and similar signs and symptoms were present. In these cases, impairment was possible at any concentration of these two drugs, but the most severe impairment was noted when the combined concentration was greater than 10 mg/L, which is still within the therapeutic range. The authors speculated that the toxicology findings in these cases resulted from recent use or overuse of the drug, but they also suggested that chronic use may be a factor, particularly in those with impaired metabolisms.

Bramness, et al. (51), reported on 62 cases of impaired driving where carisoprodol and meprobamate were the only drugs identified in the database of the Norwegian Institute of Public Health, Division for Forensic Toxicology and Drug Abuse. The study found that impaired drivers (73 percent) had higher blood carisoprodol concentrations than drivers who were not impaired (27 percent), but found no difference in blood meprobamate concentration for all the drivers viewed together. However, among occasional users of carisoprodol, there was a difference in blood meprobamate concentration between non-impaired and impaired drivers. The risk of being judged impaired rose with increasing blood carisoprodol concentration, but not with increasing blood meprobamate concentration. The clinical effects of carisoprodol as measured by the clinical test for impairment (CTI) resembled those of benzodiazepines (C-IV). Additional effects included tachycardia, involuntary movements, hand tremor and horizontal gaze nystagmus. The authors concluded that carisoprodol probably has an impairing effect by itself at blood concentration levels greater than those observed after therapeutic doses.

In 2007, Jones, et al. (52), reported the concentrations of scheduled prescription drugs found in blood samples from people arrested in Sweden during 2004 [n=7052] and 2005

[n=7759] for driving under the influence. In Sweden, both carisoprodol and meprobamate are C-IV drugs, but meprobamate is no longer registered for use. Carisoprodol was found in 66 specimens (0.9% of the total specimens); the mean concentration was 3.8 mg/l (median 2.8 mg/l and highest 11.9 mg/l) and meprobamate in 63 (0.8%) (mean concentration 15.7 mg/l, median 11 mg/l, and highest 64.0 mg/l). In eight specimens, only meprobamate was found. In twenty-seven percent of the carisoprodol cases, the blood concentrations were higher than what would be expected for normal therapeutic use (2.5-10 mg/l), thus suggesting overdose or abuse of the drug. Multi-drug use was not evaluated separately.

The FDA also noted evidence in the medical literature that the use of carisoprodol in the elderly and the nursing home population should be done with great care (53, 54). As with other CNS depressants, because of recognized age-related changes in drug metabolism and excretion and increased sedation, seniors could have an increased risk of adverse events including falls and auto accidents.

The FDA further noted that the effects induced by carisoprodol are characteristic of CNS depressants, and include altered attention, coordination, reaction time, judgment, decision making and other skills necessary to safe driving. Consequently, individuals under the influence of both therapeutic and supra-therapeutic doses of carisoprodol present a public health risk that needs to be considered when carisoprodol is prescribed. Representative cases are described below.

As documented in the scientific and medical literature, carisoprodol may produce dependence and a withdrawal syndrome characterized by anxiety, insomnia, and irritability. Moreover, in some cases, muscular pain has been described upon abrupt cessation following long-term use. See Factor 7.

Adverse Events Report in the Scientific Literature

The FDA also discussed several adverse events reported in the scientific literature. A two-year old ingested 700 milligrams (two 350 mg tablets) of carisoprodol and became increasingly drowsy over 60 minutes with symptoms progressing to lethargy and hypoxia (18). The patient's level of consciousness declined significantly requiring respiratory ventilation. Following activated charcoal and supportive care, the patient recovered fully within 12 hours.

Roberge, et al. (55), reported the case of a 52-year-old woman who presented with CNS depression and a Glasgow Coma Score of 9, secondary to ingestion of carisoprodol. She reportedly took her carisoprodol tablets in an erratic fashion (taking an estimated thirty-five extra 350 milligram tablets over a thirteen-day period) and developed stupor along with confusion and garbled speech. After administration of i.v. flumazenil (0.2 mg IV), the patient's neurologic status normalized and she required no further therapy. Carisoprodol and its metabolite meprobamate are y-aminobutyric acid receptor indirect agonists with CNS chloride ion channel conduction effects similar to the benzodiazepines, thus making flumazenil a potentially useful antidote in toxic presentations.

Siddiqi and Jennings reported the case of a near-fatal overdose involving a 40-year old male (14). The patient, who had a history of hypertension, ingested 60 carisoprodol tablets (21 grams) and an unknown quantity of chlordiazepoxide and temazepam. He developed a coma (with absent tendon and plantar reflexes), sinus tachycardia (130 bpm) with a prolonged QT interval, mild respiratory acidosis (pH 7.31; pCO2 50.1 mmHg, partially compensated with artificial ventilation), fever (100.5˚ F), hypertension (220/118 mmHg), and dry and warm skin. Following supportive care, he recovered completely without further sequelae.

Reeves, et al. (40), studied the case of a 43-year-old male who took up to 30 or more

tablets per day (a dose equal to or greater than 10,500 mg/day) of carisoprodol for several weeks, to treat chronic back and shoulder pain. After the patient abruptly stopped taking carisoprodol, he developed anxiety, tremors, muscle twitching, insomnia, auditory and visual hallucinations, and bizarre behavior. The patient was treated with olanzapine and tapering doses of lorazepam and his symptoms gradually resolved. The authors suggested that this drug withdrawal syndrome was due to the accumulation of meprobamate, the active metabolite of carisoprodol.

Bailey, et al. (47), published a retrospective analysis of drug screening performed for patient care during a six-month period at a laboratory in California. Carisoprodol was detected in the urine specimens of nineteen patients who became the study population; demographic and clinical information was then obtained by a retrospective review of the patients' medical records. In only one case was carisoprodol and/or meprobamate the sole drug(s) detected; benzodiazepines, opiates and cannabinoids were the other drugs most frequently identified.

The most common clinical abnormality was depressed levels of consciousness which occurred in twelve cases; eight patients were lethargic, three obtunded but were responsive to pain, and one obtunded and was non-responsive to pain. The clinical history suggested that in seven cases, the drug was abused or implicated in a suicide attempt or gesture. In another seven cases, the drug was used primarily for medical purposes, and in five cases, the reason for use could not be determined. Additional findings were tachycardia (eight cases), dysarthria (seven cases), hypotension (six cases), and seizure activity (five cases, including the one case where no other drugs were identified). Approximately half of the time, the patient was hospitalized. In each case, supportive care alone led to recovery. While the authors acknowledged the potential contribution of the other drugs identified to the symptomatology found in these cases, they recommended that carisoprodol and its metabolite meprobamate be included in comprehensive

drug screening as it had become an unrecognized drug of abuse in the community.

Goldberg (20) reported that manifestations of acute carisoprodol toxicity were due chiefly to stimulation and depression of the CNS. Drowsiness, dizziness, headache, diplopia, and vertigo predominated. Impaired coordination, nystagmus on lateral gaze, and an altered state of consciousness were prominent findings. Acute symptomatology was present at carisoprodol levels above 33 μg/ml, which lasted from eight to fifteen hours. Gastric lavage and supportive measures are the accepted methods of treating acute carisoprodol overdose.

Meda's Factor Six Evidence

Meda contends that scheduling carisoprodol "will have a negative impact on patient care." MX 174, at 4. According to Meda, some physicians will stop writing prescriptions for the drug and use other non-scheduled muscle relaxants due to "concerns that their prescribing may be second guessed by government regulators or law enforcement personnel." Id. According to one of Meda's Experts, he had "personally asked a number of physicians if they would use carisoprodol if scheduled, and many indicated they would not." Id.

As support for this contention, Meda also submitted two bar charts which show the percentage decrease in the number of carisoprodol prescriptions in Indiana, Nevada, Texas, and Louisiana after the drug was scheduled in these States. MX 21. More specifically, the charts show that in Indiana and Nevada, the amount of prescriptions decreased by approximately five percent following scheduling, and that in Texas and Louisiana, the amount of prescribing decreased by approximately two to three percent and four percent respectively.[37] However, in the first quarter of 2010, the number of prescriptions in Louisiana had actually increased over the

[37] According to the chart, Indiana scheduled carisoprodol on July 1, 2004, and Nevada on July 14, 2004. MX 21. However, Meda's chart shows prescribing levels only through the fourth quarter of 2005, at which time the reduction in prescribing levels in both States had begun to decrease. Id.

baseline level. Id.

Meda's evidence does not establish that scheduling carisoprodol will harm patients. As for the testimony of Meda's Expert that many physicians had told him that they would not prescribe carisoprodol and his conclusion that "a not insubstantial number would" stop prescribing, Meda's Expert produced no evidence to establish that his conclusion was based on a statistically valid sample. More specifically, Meda's Expert offered no evidence as to how many physicians he had asked, what their specialties were, how the questions were phrased, and how many had said they would stop prescribing the drug.

Likewise, the data showing a decrease in the amount of prescriptions following the scheduling of the drug in the above States do not support Meda's argument, because it assumes that the baseline level of prescribing reflects legitimate prescriptions. However, the evidence in this record clearly establishes that carisoprodol is being diverted; thus, to the extent the baseline level of prescribing includes illegitimate prescriptions, the decrease in prescriptions may reflect nothing more than doctors recognizing that certain patients are seeking carisoprodol for non-medical reasons, and are therefore being more cautious in evaluating their patients and declining to prescribe the drug to drug-seeking patients. The decrease may also reflect that doctors who have knowingly prescribed the drug for non-medical reasons have ceased this activity because the scheduling of the drug creates additional consequences for prescribing it without a medical purpose. Also, even if some doctors may have chosen to prescribe non-controlled muscle relaxants instead of carisoprodol after the drug was scheduled, this alone does not establish that patients have been harmed or that they have received "sub-optimal treatment." MX 174, at 5. In any event, as long as doctors follow accepted standards of medical practice in evaluating their patients and establish a legitimate medical purpose for prescribing carisoprodol to their patients,

they have nothing to fear from DEA. Furthermore, doctors are expected to use their best professional judgment in determining which of various drugs they should prescribe to properly treat their patients.[38]

I thus find unavailing Meda's contention that scheduling carisoprodol will create a risk to public health. To the contrary, the record contains substantial evidence establishing that the abuse of carisoprodol poses a substantial risk to those persons who abuse the drug, as well as others. See also Factor Four.

Factor 7 - Its Psychic or Physiological Dependence Potential

According to FDA, the term psychic dependence is not in current use and refers to impaired control over drug use, such as craving. This term was introduced in the late 1950's by the World Health Organization Expert Committee on Addiction-Producing Drugs, as one of the factors that, in conjunction with physical dependence, defined the addiction phenomena (Savage et al., 2003). FDA further explained that physical or physiological dependence is a form of physiologic adaptation to the continuous presence of certain drugs in the body. GX 6, at 24.

Tolerance and physical dependence examine the responses to repeated administration of a drug. Id. at 25. An assessment of tolerance or physical dependence is needed as part of the safety assessment of a drug and is a factor considered in scheduling. Id.

Tolerance is the need for increasing doses of a drug to maintain a defined effect, such as analgesia, in the absence of disease progression or other external factors. Id. Physical

[38] In its brief, Meda cites an article which states that "[d]espite concerns about the potential risk of abuse from carisoprodol because of its metabolism to meprobamate, the available literature provides no data regarding the comparative risk of abuse and addiction from skeletal muscle relaxants." Meda Br. at 48 (citing Meda Ex. 83, Chou, et al., Comparative Efficacy and Safety of Skeletal Muscle Relaxants for Spasticity and Musculoskeletal Conditions: A Systematic Review, 28 J. of Pain & Symptom Mgmt. 140, 167 (2004)). The CSA does not, however, require that the Agency (or the Secretary) conduct a comparative analysis of the abuse/addiction risk of the drugs in a therapeutic category in order to schedule a particular drug.

dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist. See American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine Consensus Document (2001). Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Id.

The FDA found that early animal drug dependence studies demonstrated that carisoprodol has a similar dependence liability to barbital, a schedule IV CNS depressant. Id. (citing FDA Reference 12). In dogs tolerant and dependent on barbital, 200 mg/kg p.o. of carisoprodol every six hours was completely effective and equivalent to 100 mg/kg of barbital in preventing the appearance of abstinence phenomena. Id.

Wyller, et al. (56), studied the occurrence of abstinence symptoms during carisoprodol withdrawal in humans. In this study, carisoprodol was gradually withdrawn over a two-week period in nine male prisoners who had been taking the drug in daily doses ranging from 700 mg to 2,100 mg for at least 9 months. Patients were assessed clinically during the withdrawal period. Most of the patients reported mental distress, such as anxiety, insomnia, and irritability. Cranial and muscular pain and vegetative symptoms were also frequently reported. Most of the symptoms observed were transient, with neither seizures nor psychotic reactions being reported.

Rohatgi, et al. (57), reported the treatment of a case of carisoprodol dependence involving a 46-year old male who self-treated his anxiety when his doctor stopped his narcotic prescriptions. The patient purchased carisoprodol over the internet and self-medicated. The patient was admitted to a treatment center and withdrawn from carisoprodol. Withdrawal

symptoms included heart palpitations, diaphoresis, chills, stomach cramps, nausea, insomnia, restlessness, myalgias, arthralgias, tremors, diarrhea, severe psychomotor agitation, feelings of depersonalization, and anxiety with suicidal ideation. The patient's symptoms were managed with risperidone, clonazepam, mirtazapine, and fluoxetine.

The FDA also noted that several other reports found that patients who abruptly stop the intake of carisoprodol may have a withdrawal syndrome. Reeves and Parker (58) studied changes in the occurrence of somatic dysfunctions in five patients during an eight-day period following discontinuation from large doses of carisoprodol. The results showed that the number of somatic dysfunctions changed significantly during the withdrawal period. Each patient had an increase in the number of somatic dysfunctions during the first three days after cessation of carisoprodol with a return to the baseline by the eighth day. This was reflected statistically in a significant-within-subjects effect for time. The results of supplemental analyses revealed a significant component of the effect and a trend for the quadratic component to be significant. Increases in the number of somatic dysfunctions during carisoprodol discontinuation support the existence of a carisoprodol withdrawal syndrome.

Finally, FDA found that the development of dependence or tolerance is also evidenced by several published reports (35, 40, 49, 57, 59). Patients increased their doses to toxic levels and appeared to be exhibiting drug-seeking behavior. FDA further found that prolonged misuse of carisoprodol can lead to physical dependence and that patients who abruptly stop carisoprodol can develop a withdrawal syndrome that includes symptoms such as anxiety, insomnia, irritability, and worsening muscular pain (40).

Subsequent to the FDA forwarding its evaluation to DEA, doctors at the Mayo Clinic

published a clinical report documenting withdrawal symptoms in a 51-year old man who was taking up to 8400 mg per day of carisoprodol, which he obtained from both his physician and an internet pharmacy, but which he had exhausted at some point before he was hospitalized.[39] GX 18, at 2. On admission, the patient "was anxious, distractable, [and] disoriented," and exhibited "[a] high frequency, postural, and kinetic tremor in [his] extremities." Id. at 1. While the patient was placed on a tapering schedule, on the third day of his hospitalization, "the patient's tremor, agitation and confusion worsened, and he experienced visual hallucinations and myoclonic jerks in the extremities." Id. at 2.

While the doctors were able to successfully treat the patient and taper him off of the drug, they concluded that "[t]his case demonstrates adverse effects of both carisoprodol toxicity and withdrawal." Id. More specifically, the authors noted that "[t]he abrupt discontinuation of high-dose carisoprodol may result in withdrawal symptoms including anxiety, psychosis, tremors, myoclonus, ataxia, and seizures." Id. The authors also opined that "[t]his withdrawal syndrome is likely under-recognized." Id.

Regarding the individual case reports, Dr. Jasinski opined that care should be taken in evaluating the significance of them because the subjects may have taken the drug for therapeutic reasons "or for non-therapeutic uses unrelated to any abuse liability," such as to commit suicide. MX 172, at 9. Dr. Jasinski further opined that the individual case reports should be considered in light of the facts that "all drugs produce untoward effects if taken at doses significantly above the recommended therapeutic dose," that a patient's having anxiety upon discontinuation of carisoprodol "could very well be a function of the interruption of effective treatment of their

[39] According to the case report, the doctors were not initially aware of the quantity of carisoprodol that the patient was taking and that he purchased it online. GX 18, at 2.

discomfort or pain," or that the "the untoward effect reported with carisoprodol" could "have been caused by other substances which the patient was" taking concurrently. Id. at 9-10.

As for Dr. Jasinski's suggestion that individual case reports should be given less weight because the patient may have taken the drug for therapeutic reasons, whether a patient initially took a drug to treat a legitimate medical condition is not relevant in assessing whether the drug causes dependence. Indeed, many patients who have become addicted to controlled substances started taking them to treat a legitimate medical condition.[40]

Moreover, while it is undoubtedly true that all drugs have "untoward effects if taken at doses significantly above the recommended therapeutic dose," the evidence establishes that patients engage in drug-seeking behavior and that the abrupt withdrawal of carisoprodol produces a withdrawal syndrome that includes a variety of symptoms such as anxiety, insomnia, irritability, tremors, and muscle pain. Contrary to Dr. Jasinski's contention that the anxiety experienced by these patients may have been caused by the interruption of effective treatment of their pain and may not be "evidence of any physical dependence," the symptoms which have been documented upon the abrupt cessation of the drug are far more extensive than anxiety.

Furthermore, several of the case reports involved patients who had taken carisoprodol for extensive periods. The prescribing information for carisoprodol states, however, that the drug "should only be used for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use has not been established." MX 6, at 2. Thus, it does not

[40] As for Dr. Jasinski's contention that the individual case reports should be given less weight because the person may have taken carisoprodol to commit suicide, I need not decide whether such evidence is probative of whether a drug has dependence liability. However, as explained above, the Senate Report expressly stated that the Agency can consider such evidence "as indicative of a drug's potential for abuse." S. Rep. 91-6134, reprinted in 1970 U.S.C.C.A.N., at 4602.

seem likely that the patients' reported anxiety upon the cessation of the drug was due to "the interruption of effective treatment of their discomfort or pain." MX 172, at 10.[41]

Finally, in October 2009, based on new safety information, the FDA required that Meda make several changes to the approved label. The first of these involved the insertion of a sentence into section 5.2 (entitled "Drug Dependence, Withdrawal, and Abuse") that "there have been post-marketing-adverse event reports of SOMA associated abuse when used without other drugs with abuse potential." MX 30, at 5. Thus, this section of the label now states:

> In the postmarketing experience with SOMA, cases of dependence, withdrawal, and abuse have been reported with prolonged use. Most cases of dependence, withdrawal, and abuse occurred in patients who have had a history of addiction or who used SOMA in combination with other drugs with abuse potential. However, there have been post-marketing-adverse event reports of SOMA associated abuse when used without other drugs with abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. To reduce the chance of SOMA dependence, withdrawal, or abuse, SOMA should be used with caution in addiction-prone patients and in patients taking other CNS depressants including alcohol, and SOMA should not be used more than two to three weeks for the relief of acute musculoskeletal discomfort.
>
> Soma, and one of its metabolites, meprobamate (a controlled substance), may cause dependence.

MX 6, at 2.[42] The FDA also required that Meda change the label to include the following statement:

> SOMA is not a controlled substance . . . .

[41] As for the contention that in two of the case reports, "the untoward effect reported with carisoprodol would appear to have been caused by other substances the patient had taken concurrently," Dr. Jasinski identified these reports only by their exhibit numbers and the publication they appeared in. See MX at 172, at 10 (citing MXs 110 & 161). However, neither of these exhibits was entered into evidence. I thus cannot evaluate the validity of Dr. Jasinski's contention.

[42] With the exception of the third sentence ("However, there have been post-marketing adverse reports of SOMA-associated abuse when used without other drugs with abuse potential.]"), this portion of the label repeats verbatim the 2007 label. See MX 25, at 5.

> Discontinuation of carisoprodol in animals or in humans after chronic administration can produce withdrawal signs, and there are published case reports of human carisoprodol dependence.
>
> In vitro studies demonstrate that carisoprodol elicits barbiturate-like effects. Animal behavior studies indicate that carisoprodol produces rewarding effects. Monkeys self administer carisoprodol. Drug discrimination studies using rats indicate that carisoprodol has positive reinforcing and discriminative effects similar to barbital, meprobamate, and chlordiazepoxide.

See MX 30, at 8; MX 6, at 3. While Meda initially objected to the proposed changes, it eventually agreed to them. MX 30, at 1.

I therefore conclude that substantial evidence supports a finding that carisoprodol has dependence liability similar to that of barbital, a schedule IV CNS depressant.

Factor 8 - Whether the Substance is an Immediate Precursor of a Substance already Controlled

Carisoprodol metabolizes to meprobamate, a schedule IV controlled substance. However, the FDA found that carisoprodol is not an immediate precursor of meprobamate or any other controlled substance. GX 6, at 26.

CONCLUSIONS OF LAW

Under 21 U.S.C. 811(a)(1)(a), to "add" a drug to one of the schedules of controlled substances, the Agency must first find that carisoprodol "has a potential for abuse." If such a finding is supported by the record, the Agency must then make the "findings prescribed by subsection 812 of this title for the schedule in which such drug is to be placed." 21 U.S.C.811(a)(1)(B). Having considered all eight of the section 811(c) factors, I conclude that a preponderance of the evidence supports the conclusion that carisoprodol "has a potential for abuse" such as to warrant control and that it should be placed in schedule IV.

The Section 811(a)(1)(a) Finding – Carisoprodol Has A Potential For Abuse

A preponderance of the evidence supports the conclusion that carisoprodol has a potential for abuse, and indeed, is being widely abused.[43] The NSDUH data establish that a large number of persons are taking carisoprodol on their own initiative rather than on the basis of a physician's recommendation. The NSDUH data - which Meda's Expert acknowledged was generally reliable - consistently show that between 2.5 and 2.8 million persons have used carisoprodol for non-medical reasons, including approximately 1 million 18-25 year olds, and more than 100,000 12-17 year olds. As explained above, given the magnitude of the nonmedical use of carisoprodol, the Agency is not required to show that the rate of abuse is increasing in order to support a finding that the drug has a potential for abuse such as to warrant control.[44]

In addition, the evidence shows that individuals are taking carisoprodol in amounts sufficient to create a hazard to the health and safety of both themselves and others. Notwithstanding the criticism of the DAWN data, the estimates as to the number of emergency

[43] In both its brief and its exceptions, Meda notes that "DEA did not present any witnesses from FDA to justify their findings or . . . provide [it with] an opportunity . . . to challenges the bases for such witnesses' findings." Meda's Exceptions at 1. It further argues that it has been denied a meaningful hearing because it "never had an opportunity to challenge the medical and scientific findings that formed the basis of the scheduling determination." Id. at 2. See also Meda. Br. at 22. ("DEA counsel did not call any HHS or FDA witness to testify and justify the scientific, medical, and legal basis underlying the HHS recommendations. No FDA or HHS witness was made available to answer questions about the numerous weaknesses in the data cited [by the FDA], or otherwise explain the FDA analysis and conclusions.").

As explained above, many of HHS's findings were based on published articles, and Meda raises no contention that any unpublished articles cited by HHS were not provided to it. Meda does not explain why additional testimony was required to explain the contents of the articles. Moreover, Meda's Experts testified as to various issues with both the Government's data sources and the FDA's reliance on several articles. In addition, Meda does not contend that it sought (and was denied) a subpoena to require the testimony of any FDA employees who were involved in preparing the report. I thus reject Meda's contention.

[44] In its brief, Meda also cites to admittedly anecdotal evidence that an analysis by RADARS of website postings in Erowid, "an online member-supported organization where individuals anonymously post [their] experiences with psychoactive substances, including prescription drugs," and that Skelaxin, another muscle relaxant, "was among the ten most frequently mentioned prescription drugs [but] carisoprodol was not." Meda Br. 35. Contrary to Meda's understanding, whether Skelaxin is being abused more often than carisoprodol is irrelevant in assessing whether the latter has "a potential for abuse" and warrants control. 21 U.S.C. 811(a). It is further noted that while Meda cites the RADARS analysis as an exhibit, see Meda Br. 97 (citing Meda Exh. 15), the record does not contain this exhibit.

room visits related to carisoprodol are comparable to those for diazepam, a schedule IV controlled substance.

Next, data obtained from the Florida Medical Examiners Commission for the years 2004 through 2008, establish that carisoprodol (or its metabolite meprobamate) was the cause of death in between 74 and 96 cases each year. It bears noting that this is but one State's data.

Also, NPDS data for the years 2006 and 2007 show that carisoprodol (as a sole drug) has been involved in more than 3500 toxic exposures cases. Of these, between 2687 and 2821 cases were serious enough to require treatment in a health care facility, and in more than 100 cases, the patient had life-threatening symptoms or a significant residual disability.

Finally, while Meda notes that data from the FDA AERS system show that, between January 1979 and May 2001, "only 83 reports" have "included the terms abuse, dependency, or withdrawal," and that this must be compared with the total number of carisoprodol prescriptions, these data are compiled from reports which have been voluntarily submitted by consumers and health care professionals. Thus, these data likely substantially underreport the number of such incidents.

The evidence further shows that there is significant diversion of carisoprodol from legitimate channels. First, NFLIS data show that carisoprodol has consistently ranked among the top twenty-five drugs which have been analyzed and identified by forensic laboratories following seizures which occurred during the course of criminal investigations. Moreover, because carisoprodol is controlled in only seventeen States, which comprise approximately thirty-five percent of the United States' population, and as Meda's expert recognized, the likelihood of a sample "being analyzed is substantially affected by the prosecutor's perceptions of the available

criminal charges," it is likely that the NFLIS data substantially understate the extent to which carisoprodol is being found during criminal investigations.

Of particular significance, the testimonies of the DEA Deputy Assistant Administrator; a Tennessee Bureau of Investigation Special Agent in Charge, who was the former Coordinator of the Tennessee Drug Diversion Task Force; and the Executive Director of the Ohio State Board of Pharmacy; provide substantial evidence that carisoprodol is being unlawfully distributed, typically with narcotics and benzodiazepines, and is being abused. These officials testified that carisoprodol is being distributed by: 1) internet pharmacies based on prescriptions issued by doctors who never see their patients; 2) doctors, who while they meet their patients, either perform no physical exam or a cursory physical examination; and 3) street dealing. The Executive Director of the Ohio Board also testified to data obtained through the Board's prescription monitoring program showing that persons are engaging in doctor shopping to obtain large quantities of the drug. The officials also testified to the practice of drug abusers using carisoprodol as part of a cocktail which includes narcotics (such as oxycodone and hydrocodone) and benzodiazepines.

While carisoprodol is indicated for only short-term use of up to two to three weeks, prescription data for a recent five-year period show that more than 25 percent of patients used the drug for more than one month and 4.3 percent used the drug for more than 360 days. Similarly, Bramness, who studied carisoprodol use and abuse in Norway (where the drug is only approved for use of up to one week) during 2004, found that 8 percent of the patients who obtained the drug were also abusing benzodiazepines and 14 percent of the patients were also abusing opioids. Moreover, while those patients who were using carisoprodol for therapeutic purposes received only 12 percent of the carisoprodol which was dispensed, the opioid abusers received

48 percent. Of further note, 14 percent of the patients had received an amount of the drug equal to 75 daily doses or more.

While Meda cites both the Fraser study (in particular, the third arm) and its recent clinical trials, both items of evidence suffer from significant limitations and are of limited probative value. As noted above, the third arm of the Fraser study, involved only five patients (only one of whom received the drug for 54 days), and Meda's recent clinical trials involved only short term use at therapeutic levels. Accordingly, I conclude that the record as a whole establishes that carisoprodol has a potential for abuse (and is being abused at such a level) as to warrant control. See 21 U.S.C. 811(a)(1).

The Section 812(b) Placement Findings

The FDA recommended that carisoprodol be placed in schedule IV. Under 21 U.S.C. 812(b), the Attorney General is required to make the following findings to do so.[45] These are:

> (A) The drug . . . has a low potential for abuse relative to the drugs or other substances in schedule III.
> (B) The drug . . . has a currently accepted medical use in treatment in the United States.
> (C) Abuse of the drug . . . may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

21 U.S.C. 812(b)(4).

It is undisputed that carisoprodol has a currently accepted medical use in treatment in the United States and is FDA-approved for the relief of discomfort associated with acute, painful musculoskeletal conditions. GX 6, at 26.

The FDA further found that carisoprodol has a low potential for abuse relative to schedule III controlled substances. Id. FDA found that carisoprodol is a CNS (central nervous system) depressant and that it is abused primarily in combination with other drugs of abuse

[45] While Meda challenged the Government's (and FDA's) finding that carisoprodol has a potential for abuse such as to warrant control, it did not challenge the FDA's placement findings. See Meda's Br. at 111-14.

including opioids and benzodiazepines, cocaine, and marijuana. Id. Carisoprodol metabolizes into meprobamate, a schedule IV controlled substance. Based on the DAWN ED estimates, FDA calculated an abuse frequency which suggests that carisoprodol is being abused at a rate similar to that of diazepam, a schedule IV controlled substance. See 21 CFR 1308.14(c). In vitro studies demonstrate that carisoprodol has an affinity for the GABAα receptor and elicits barbiturate-like effects. Likewise, in a drug-discrimination study, carisoprodol was completely effective in preventing abstinence syndrome in dogs tolerant and dependent on barbital, a schedule IV controlled substance. In a study involving rats trained to discriminate carisoprodol, various controlled substances including meprobamate, pentobarbital (C-II/C-III), and chlordiazepoxide (C-IV), substituted fully for the discriminative stimulus effects of carisoprodol. In a further study, bemegride, a barbiturate antagonist, antagonized the discriminative stimulus effect of carisoprodol in rats trained to discriminate the drug. While Meda's Expert opined that these studies do not establish carisoprodol's abuse liability,[46] he acknowledged that they do indicate that carisoprodol may have effects similar to those of barbiturates.

In addition, several human studies establish that carisoprodol has effects similar to that of CNS depressants. Most significantly, Bramness, et al., found that the clinical effects of carisoprodol resemble those of benzodiazepines, which are schedule IV controlled substances. I therefore hold that substantial evidence supports the FDA's conclusion that carisoprodol has a low potential for abuse relative to the drugs or other substances in schedule III. See Grinspoon, 828 F.2d at 894 (upholding Agency's reliance of on studies which suggested that MDMA was "related in its effects to" other schedule I and II controlled substances).

[46] As found above, the record as a whole establishes that carisoprodol has a potential for abuse and is being abused. I note Dr. Jasinski's testimony that the animal studies do not establish carisoprodol's abuse liability only to provide context to his acknowledgement that the animal studies indicate that carisoprodol may have effects similar to those of barbiturates.

Finally, the FDA concluded that the abuse of carisoprodol may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III. GX 6, at 27. In support of its conclusion, the FDA noted that upon the withdrawal of barbital from dogs dependent on it, carisoprodol prevents the abstinence syndrome. Id. FDA also cited case studies which show that carisoprodol causes psychological or physical dependence and that "carisoprodol produces a withdrawal syndrome characterized by clinical depression, anxiety, drug craving, irritability and poor concentration." Id.

The record contains substantial evidence to support the FDA's conclusion. Meda cites both the Fraser study and its recent clinical trials as evidence that carisoprodol does not cause dependence. However, the Fraser study expressly noted that "it remains to be seen whether administering carisoprodol continuously in larger doses would induce" a barbiturate-like withdrawal pattern upon discontinuation of the drug. Likewise, Meda's clinical trials involved administration of the drug for no more than two-weeks and at therapeutic levels. Moreover, Meda eventually agreed to change the drug label to reflect that "cases of dependence [and] withdrawal . . . have been reported with prolonged use." MX 6, at 2.

A case study by Reeves found that when a 43-year-old male, who had taken large doses for several weeks, stopped taking carisoprodol, he developed anxiety, tremors, muscle twitching, insomnia, auditory and visual hallucinations and engaged in bizarre behavior. In a study of nine male prisoners who had been taking carisoprodol in doses of 700 to 2100 mg for at least nine months, Wyller found that when the drug was gradually withdrawn over a two-week period, most of the patients reported mental distress including anxiety, insomnia, and irritability; cranial and muscular pain, as well as vegetative symptoms, were also frequently reported. Rohatgi reported the case of a 46-year old male who purchased carisoprodol over the internet and self-

medicated to treat his anxiety after his physician stopped his narcotic prescriptions. Upon the patient's admission to a treatment center and being withdrawn from the drug, the patient exhibited heart palpitations, diaphoresis, chills, stomach cramps, nausea, insomnia, restlessness, myalgias, arthralgias, tremors, diarrhea, severe psychomotor agitation, feelings of depersonalization, and anxiety with suicidal ideation. The FDA also cited five other published studies which evidence that persons taking carisoprodol can become physically dependent and engage in drug-seeking behavior.

Finally, a case study published by physicians at the Mayo Clinic subsequent to the FDA's report documented the presence of withdrawal symptoms in a 51-year old man who had taken up to 8400 mg per day before he exhausted his supply (which he obtained from both his physician and the internet). Upon his admission, the patient "was anxious, distractable, [and] disoriented," and exhibited "[a] high frequency, postural, and kinetic tremor in [his] extremities." The patient was placed on a tapering schedule, but on the third day, his "tremor, agitation and confusion worsened, and he experienced visual hallucinations and myoclonic jerks in the extremities." While the doctors were able to successfully taper the patient off of the drug, they concluded that "[t]he abrupt discontinuation of high-dose carisoprodol may result in withdrawal symptoms including anxiety, psychosis, tremors, myoclonus, ataxia, and seizures."

In its Exceptions, Meda argues that the ALJ unfairly and unjustifiably relied on this study, which the Government introduced to rebut Dr. Jasinski's testimony. Exceptions at 2-3. Meda objects that the document was offered after the ALJ had excused the last witness, thereby depriving it "of any opportunity to subject the document to expert scrutiny." Id. at 2. Meda also objects that the ALJ gave this report "significant weight" and "incorrectly elevated [it] to that of a 'study.'" Id. (citing ALJ 34, 85).

However, Dr. Jasinski acknowledged that abuse of carisoprodol over a prolonged period could lead to limited physical or psychological dependence. Tr. 706-07. While Dr. Jasinski further maintained that this was "not the specific issue" and that "[t]he specific issue [is whether abuse] would lead to drug seeking or . . . to a severe withdrawal syndrome," id., his view of the statute is mistaken. Under subsection 812(b), a finding that abuse of a drug "may lead to severe psychological or physical dependence" is only required if the drug is to be placed in schedule II. 21 U.S.C. 812(b)(2)(C). By contrast, to place a drug in schedule IV, the necessary finding requires only that abuse of the drug "may lead to limited physical dependence or psychological dependence relative to the drugs . . . in schedule III." Id. 812(b)(4)(C).

Even if - given Dr. Jasinski's acknowledgment that abuse of carisoprodol may lead to limited physical or psychological dependence - the article does not constitute valid rebuttal, Meda cannot claim that its admission to the record was prejudicial. The article (which had not been published at the time the parties exchanged their pre-hearing statements) is consistent with other case studies which Dr. Jasinski had ample opportunity to criticize and was therefore cumulative. While the ALJ did mischaracterize the report as the "Mayo Clinic data," ALJ at 101, it is just one of several clinical reports/case studies that supports the conclusion that prolonged abuse of carisoprodol may lead to limited physical or psychological dependence, as Dr. Jasinski acknowledged. I thus find that the abuse of carisoprodol "may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III." 21 U.S.C. 812(b)(4)(C). Accordingly, I further find that substantial evidence supports the FDA's recommendation that carisoprodol be placed in schedule IV.

Regulatory Requirements

Effective [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER][47], carisoprodol will be placed in schedule IV of the Controlled Substances Act. Thereafter, any person who engages in the manufacture, distribution, dispensing, importing, exporting, as well as any person who possesses the drug will be subject to the provisions of the Act and DEA regulations, including the Act's administrative, civil, and criminal sanctions which are applicable to schedule IV controlled substances. These include the following:

Registration. Any person who manufactures, distributes, dispenses, imports, exports, engages in research or conducts instructional activities or chemical analysis with carisoprodol, must be registered to conduct such activities in accordance with 21 CFR Part 1301. Any person who is currently engaged in any of the above activities must submit an application for registration by [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER] and may continue their activities until DEA has approved or denied that application.

Disposal of Stocks. Any person who elects not to obtain a schedule IV registration, or who is not entitled to such registration, must surrender all quantities of currently held carisoprodol in accordance with the procedures of 21 CFR 1307.21, on or before [INSERT DATE 30 AFTER PUBLICATION IN THE FEDERAL REGISTER], or may transfer all quantities of currently held carisoprodol to a person registered under the CSA and authorized to possess schedule IV controlled substances, on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. Any carisoprodol surrendered to DEA must be listed on a DEA Form 41, "Inventory of Controlled Substances Surrendered for Destruction."

[47] I have considered the comments of the Healthcare Distribution Management Association in setting the effective dates with respect to each of the various requirements.

DEA Form 41 may be obtained at http://www.deadiversion.usdoj.gov/21cfr_reports/surrend/ , or from the nearest DEA office.

Security. Carisoprodol will be subject to the security requirements applicable to controlled substances in schedules III through V including 21 CFR 1301.71, 1301.72(b), (c), and (d), 1301.73, 1301.74, 1301.75(b) and (c), 1301.76, and 1301.77. The requirements of 21 CFR 1301.71, 1301.72(d), 1301.74, 1301.75(b) and (c), and 1301.76 shall be applicable to carisoprodol [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. The requirements of 21 CFR 1301.72(b) and (c), 1301.73, and 1301.77 shall be applicable to carisoprodol [INSERT DATE 120 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Labelling and Packaging. All commercial containers of carisoprodol that are packaged on or after [INSERT DATE 120 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER] shall be labeled as C-IV and packaged in accordance with 21 CFR 1302.03-1302.07. Commercial container packaged before [INSERT DATE 120 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER] and not meeting the requirement of 21 CFR 1302.03-1302.07 may be distributed until [INSERT DATE 180 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. On or after [INSERT DATE 180 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER] all commercial containers of carisoprodol must be labeled as C-IV and comply with 21 CFR 1302.03-1302.07.

Inventory. Pursuant to 21 CFR 1304.03, 1304.04, and 1304.11, every registrant who is required to keep records and who possesses any quantity of carisoprodol shall take an initial inventory of all stocks of carisoprodol on hand on or before [INSERT DATE 30 DAYS AFTER

PUBLICATION IN THE FEDERAL REGISTER.]. Thereafter, carisoprodol shall be included in each inventory made by the registrant pursuant to 21 CFR 1304.11(c).

Records. All registrants are required to keep records pursuant to 21 CFR 1304.03, 1304.04, 1304.21, 1304.22, and 1304.23, after [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Prescriptions. All prescriptions for carisoprodol or prescriptions for products which contain carisoprodol shall comply with 21 CFR 1306.03-1306.06, 1306.21, and 1306.22-1306.27, after [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Importation and Exportation. All importation and exportation of carisoprodol is subject to 21 CFR Part 1312, after [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Criminal Liability. Any activity with carisoprodol not authorized by, or conducted in violation of, the Controlled Substances Act or the Controlled Substances Import and Export Act, occurring on or after [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTRATION] is unlawful.

Regulatory Analyses

Executive Orders 12866 and 13563

In accordance with 21 U.S.C. 811(a), this scheduling action is subject to formal rulemaking procedures done "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of

Management and Budget pursuant to Section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

Regulatory Flexibility Act

The Administrator hereby certifies that this rulemaking has been drafted in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612), has reviewed this regulation, and by approving it certifies that this regulation will not have a significant economic impact on a substantial number of small entities.

In considering the economic impact on small entities, the first question is whether a substantial number of small entities are affected. In this instance, the entities affected are those now selling carisoprodol-containing products that do not hold a DEA registration. DEA identified 22 firms that are manufacturing carisoprodol-containing products. 74 FR at 59111. Fifteen of these firms hold DEA registrations, leaving seven firms that sell carisoprodol and do not hold a registration. DEA has no information on the number of non-registrants engaged in the distribution or importation of carisoprodol, but there is reason to believe that the number of such firms is well in excess of the seven already identified. The Small Business Administration size standard for a small wholesaler of drugs is 100 employees. It is clearly possible to operate a drug distribution firm with fewer than 100 employees. Therefore, a substantial number of small entities will be affected by this rule.

The economic impact on non-registrants now selling carisoprodol will occur in two ways: the cost of registration and the cost of meeting the security requirements in 21 CFR Part 1301. There is also a potential economic impact on those firms that do not currently distribute carisoprodol but which might wish to enter the market.

The annual registration fee for a distributor, importer, or exporter is $1,147. There is some uncertainty in estimating the cost of meeting the security requirements, because most non-registrants already meet the security requirements, at least in part, for schedule III and IV substances. A conservative estimate assumes that every non-registrant will have to buy a safe to store carisoprodol. A safe with a capacity of 13.5 cubic feet should be adequate and may be purchased for approximately $1,350, which, when annualized over 15 years at 7.0 percent, results in a cost of $148 per year. Therefore, the total annual cost of compliance with this rule is $1,295.

The usual standard for a significant economic impact is 1.0 percent of revenue. For $1,295 per year to be a significant economic impact, a firm's annual revenue would have to be less than $130,000. Any firm in the drug distribution business would need annual revenue well in excess of this amount to sustain itself.

It is acknowledged that, for a small firm, there may be some inconvenience and expense in preparing the necessary forms to obtain and renew a registration. These are minor costs. There are also recordkeeping requirements, but these will impose little or no incremental cost for a firm that is already maintaining the records needed for a wholesale business. Accordingly, the costs of registration and the security requirements will not cause a significant economic impact.

If a firm chooses not to register and to drop its carisoprodol line, the cost to the firm would exceed its earnings on its carisoprodol sales. The firm may also lose some customers who do not want to buy from a distributor that does not carry carisoprodol. A competent manager will recognize this cost, and in light of the small cost of registering, would presumably choose to drop carisoprodol from the firm's product line only if the firm was earning a negligible profit from its carisoprodol sales and dropping the product would not result in the loss of significant customers.

Accordingly, DEA finds that this rule will not have a significant economic impact on a substantial number of small entities.[48]

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.

Executive Order 13132

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

Executive Order 13175

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

Paperwork Reduction Act of 1995

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

Unfunded Mandates Reform Act of 1995

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

[48] In the Notice of Proposed Rulemaking, DEA noted that it had no information regarding the number of persons who may distribute carisoprodol-contain products, but who do not manufacture, package, repackage, or relabel these products and sought comments from any entities that might be affected by this action. See 74 FR 59111. No commenter provided such information.

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). This rule will not result in an annual effect on the economy of $100,000,000 or more, a major increase in costs or prices, or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets.

List of Subjects in 21 CFR Part 1308

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

Under the authority vested in the Attorney General by section 201(a) of the CSA (21 U.S.C. 811(a)), and delegated to the Administrator of the Drug Enforcement Administration pursuant to 28 CFR 0.100, 21 CFR Part 1308 is amended to read as follows:

PART 1308-SCHEDULES OF CONTROLLED SUBSTANCES

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

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

2. Section 1308.14 is amended by redesignating paragraphs (c)(5) through (c)(52) as paragraphs (c)(6) through (c)(53) and adding a new paragraph (c)(5) to read as follows:

§ 1308.14 Schedule IV.

* * * * *

(c) * * *

(5) Carisoprodol 8192

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Dated: November 18, 2011

Michele M. Leonhart
Administrator

NOTE: The following appendixes will not publish in the Code of Federal Regulations.

APPENDIX A

States in which Carisoprodol is a Controlled Substance and their Population

STATE	POPULATION
Oklahoma	3,751,351
Hawaii	1,360,301
Kentucky	4,339,367
New Mexico	2,059,179
Oregon	3,831,074
Georgia	9,687,653
Arkansas	2,915,918
Alabama	4,779,736
West Virginia	1,852,994
Florida	18,801,310
Arizona	6,392,017
Indiana	6,483,802
Nevada	2,700,551
Louisiana	4,533,372
Texas	25,145,561
Utah	2,763,885
Washington	6,724,540
Total	**108,122,611***

Total 2010 population = 307,006,556 (source www. uscensus2010data.com)

* 35.22 % of total population of United States

APPENDIX B

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