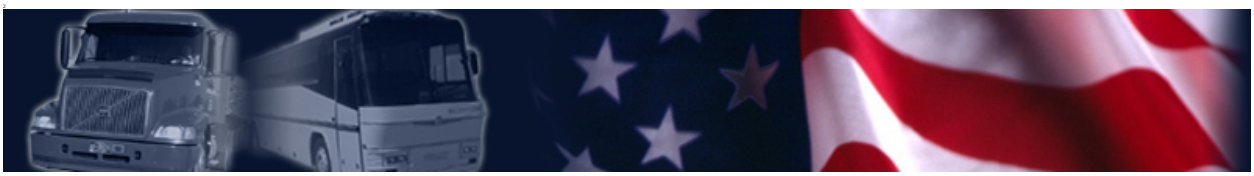

Expert Panel Commentary and Recommendations:
Licit Schedule II Drug Use and Commercial Motor Vehicle Driver Safety (Comprehensive Review)

Presented to

Physical Qualifications Division

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Introduction

Section 4116 of the Safe, Accountable, Flexible, Efficient Transportation Equity Act: A Legacy for Users (SAFETEA-LU, Pub. L. 109-59) requires the Secretary of Transportation, with the advice of the recently established Medical Review Board (MRB) and a Chief Medical Examiner, to "establish, review, and revise medical standards for operators of commercial motor vehicles (CMVs) that will ensure that the physical condition of operators is adequate to enable them to operate the vehicles safely."

In providing this advice, the MRB is charged initially with reviewing all current Federal Motor Carrier Safety Regulations (FMCSRs) medical standards (CFR 391.41) and associated guidelines to help Federal Motor Carrier Safety Administration (FMCSA) determine the effort needed to make them consistent with current medical knowledge. This may lead to the revision of the existing structure or to new standards and guidelines to ensure that drivers operating CMVs in interstate commerce, as defined in CFR 390.5, are physically qualified to do so. FMCSA requires that guidance from the MRB be science-based and represent best practice.

In support of the MRB's task, FMCSA has convened panels of experts charged with reviewing scientific evidence addressing questions of importance to FMCSA. Panel members are identified by FMCSA through a national recruitment effort and are objectively ranked and selected for having sufficient expertise in the topic area and no scientific or financial conflicts of interest. The scientific evidence is presented to the expert panel in the form of a systematic review of published literature conducted by FMCSA's support contractor (ECRI under subcontract to MANILA Consulting). Such reviews are comprehensive examinations of scientific literature, including appropriate quantitative analyses, for the specific FMCSA-identified occupational health issue and questions under investigation. Each review is presented in draft form for comment by the panel members and is intended to serve as the scientific base for recommendations and guidance produced by the expert panel.

FMCSA commissioned a systematic review to inform the MRB on issues relevant to use of Schedule II drugs by CMV drivers. The current FMCSR medical standards, CFR 391.41, include the following statements regarding the physical qualifications for drivers:

> (a) A person shall not drive a commercial motor vehicle unless he is physically qualified to do so and, except as provided in §391.67, has on his person the original or a photographic copy of a medical examiner's certificate stating he or she is physically qualified to drive a commercial motor vehicle.
>
> (b) A person is physically qualified to drive a motor vehicle if that person…

The regulations relevant to Schedule II drugs go on to state that:

> A person is physically qualified to drive a commercial motor vehicle if that person (b)(12)(i) Does not use a controlled substance identified in 21 CFR 1308.11 Schedule I, an amphetamine, a narcotic, or any other habit-forming drug.
> (b)(12)(ii) *Exception*. A driver may use such a substance or drug, if the substance or drug is prescribed by a licensed medical practitioner who:

> (b)(12)(ii)(A) Is familiar with the driver's medical history and assigned duties; and
> (b)(12)(ii)(B) Has advised the driver that the prescribed substance or drug will not adversely affect the driver's ability to safely operate a commercial motor vehicle;

FMCSA has produced medical advisory criteria to assist medical examiners in implementation of the regulations. The advisory criteria state: “Unlike regulations which are codified and have a statutory base, the recommendations in this advisory are simply guidance established to help the medical examiner determine a driver’s medical qualifications pursuant to Section 391.41 of the FMCSRs (FMCSRs). The Physical Qualifications Division routinely sends copies of these guidelines to medical examiners to assist them in making an evaluation. The medical examiner may, but is not required to, accept the recommendations. Section 390.3(d) of the FMCSRs allows employers to have more stringent medical requirements.”

In regard to §391.41 (b)(12)(i) and (ii), the Medical Advisory Criteria state:

> This exception does not apply to the use of methadone.
>
> The intent of the medical certification process is to medically evaluate a driver to ensure that the driver has no medical condition which interferes with the safe performance of driving tasks on a public road. If a driver uses a Schedule I drug or other substance, amphetamine, a narcotic, or any other habit-forming drug, it may be cause for the driver to be found medically unqualified. Motor carriers are encouraged to obtain a practitioner's written statement about the effects on transportation safety of the use of a particular drug.
>
> A test for controlled substances is not required as part of this biennial certification process. The FMCSA or the driver's employer should be contacted directly for information on controlled substances and alcohol testing under Part 382 of the FMCSRs.
>
> The term “uses” is designed to encompass instances of prohibited drug use determined by a physician through established medical means. This may or may not involve body fluid testing. If body fluid testing takes place, positive test results should be confirmed by a second test of greater specificity. The term "habit forming" is intended to include any drug or medication generally recognized as capable of becoming habitual, and which may impair the user's ability to operate a commercial motor vehicle safely.
>
> The driver is medically unqualified for the duration of the prohibited drug(s) use and until a second examination shows the driver is free from the prohibited drug(s) use. Recertification may involve a substance abuse evaluation, the successful completion of a drug rehabilitation program, and a negative drug test result. Additionally, given that the

certification period is normally 2 years, the examiner has the option to certify for a period of less than 2 years if this examiner determines more frequent monitoring is required.

FMCSA commissioned the systematic review and evidence report to examine the relationship between the licit use of a Schedule II drug and the risk of a motor vehicle crash. In order to meet these aims, the following eight questions were addressed:

Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Key Question 2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

Key Question 3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?

Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

Key Question 7: Are there common drug interactions with any a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

Key Question 8: Are there common drug interactions with any a prescribed Schedule II drug that affect indirect measures of driving ability?

The draft evidence report was provided to a panel of five experts one month in advance of the proceedings, which were held September 19–21, 2006. During the proceedings, the methodology used to produce the report and the findings for each key question were presented and discussed. The panel then produced commentary in response to the findings through a process known as the nominal group technique. This technique requires that each panel member develop statements in response to the issues and findings presented in the report. Individual statements are then consolidated into a commentary on findings, with the requirement that all panel members endorse the final statement.

In addition to commentary regarding the findings of the systematic review, panel members produced commentary regarding recommendations for further study relevant to CFR 391.41 (b)(12)(i) and (ii).

Panel members agreed that two important principles warranted emphasis in these proceedings. First, they noted that CMV drivers *must* be held to a higher safety standard than drivers of noncommercial vehicles. Considerations leading to this higher standard include the greater exposure (miles driven and consecutive hours of driving), size and weight of vehicle and cargo, the numerous external demands placed on CMV drivers (which potentially impact the effect of drugs and the driver's ability to comply with the prescribed schedule and precautions), the driving environment and the potentially hazardous cargo transported by many CMV drivers. Second, the panel members noted that while certain Schedule II drugs

may not impair driving ability in any given healthy individual study subject, the assessment of driving safety for a CMV driver taking a Schedule II drug must also include an assessment of the underlying medical condition for which it is prescribed, any coexisting medical conditions, and additional medications the individual is or may be taking. Panel members noted that medical examiners frequently encounter applicants being treated by their medical practitioners with potentially impairing medications including, but not limited to, Schedule III and IV narcotics and benzodiazepines. The panel strongly encouraged FMCSA to evaluate the risk of these medications as well.

Panel members commented on the current lack of consistency in training and knowledge of medical examiners. Once this lack of consistency has been addressed through other programs (i.e., the National Registry of Medical Examiners and a certification program), these recommendations may need to be revisited. The statements in this document address the current situation.

Commentary on Findings of the Systematic Review

Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Evidence Report Findings

1. **A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether there is a relationship between the licit use of a Schedule II drug and motor vehicle (any category) crash risk.**

   Although our searches identified and retrieved 49 potentially relevant articles, none met the inclusion criteria for this key question. The primary reason for exclusion was that studies combined crash data from licit and illicit Schedule II drug users (32 studies). Because illicit drug users do not use drugs in a manner that is compatible with a therapeutic regimen (the aim of a drug abuser is to use the drug to deliberately initiate a change in mental state whereas, the aim of a licit user is to treat a disorder), crash data including drug abusers cannot provide an answer to Key Question 1. The second most common reason for exclusion was that several studies were designed to examine the crash risk associated with a particular drug class encompassing drugs that spanned several drug schedules (eight studies). Not all opioids, stimulants, and depressants are Schedule II drugs and studies that evaluated crash risk by drug class did not stratify crash risk data by the United States Drug Enforcement Agency (DEA) drug schedule.

Expert Panel Statement

The expert panel was concerned that a paucity of data meeting the inclusion criteria precluded it from drawing an evidence-based conclusion regarding whether there is a relationship between the licit use of a Schedule II drug and motor vehicle (any category) crash risk. Several members of the panel argued that data from studies in which crash data for individuals did not distinguish between licit and illicit use of Schedule II drugs should be considered by FMCSA in answering this question. Panel members were in agreement that the studies examining crash data for individuals legally using prescribed narcotics, stimulants,

and depressants but in which crash risk data were not stratified by the DEA drug schedule should be given further consideration (Table 1). The panel thought that the study by Leveille, which found the odds of using opioids among people who crashed to be greater than the odds of using opioids among those who did not crash, to be of relevance, even though the opioids were not all in Schedule II. In the absence of crash data specifically addressing the licit use of Schedule II drugs, panel members expressed willingness to base decisions on surrogate measures of driving ability, including simulated driving performance and measures of cognitive and psychomotor function.

Table 1. Studies Examining Crash Risk with Licit use of Mixed-Schedule (II–IV) Controlled Substances

Reference	Year	Study design	Outcome Assessed	Relevant Drug Group	*Finding*
Leveille et al.	1994	CCS	% of crashers taking drug vs. % of non-crashers taking drug	Opioids	*OR = 1.8 (1.0 to 3.7)*
Ray et al.	1992	CCS	% of crashers taking drug vs. % of non-crashers taking drug	Opioids/antihistamines	*RR = 1.1 (0.7 to 1.8)*
Lesch et al.	1989	CCS	% of crashers taking drug vs. % of non-crashers taking drug	Tranquilizers/hypnotics/sedatives	*No sig. diff.*
				Analgesics/spasmolytics	*No sig. diff.*
Honkanen et al.	1980	CCS	% of crashers taking drug vs. % of non-crashers taking drug	Psychotropic agents	*P = 0.03 for diazepam*
				Analgesics	*No sig. diff.*

***Key Question 2:* Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?**

Evidence Report Findings

General Finding

1. **A paucity of data from studies that enrolled CMV drivers precludes one from directly determining whether the driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior of CMV drivers is adversely effected by the licit use of any Schedule II opioids.**

   Two included studies enrolled individuals who could potentially be considered to be CMV drivers. Both studies recruited individuals whom the study investigators termed, "professional drivers." It is not clear from the articles describing these studies, however, how the study investigators defined a "professional driver." Consequently, it remains a possibility that none, or only a small proportion, of the enrollees in these two studies actually drove large trucks or buses.

Expert Panel Statement

Members of the panel acknowledge that the medical literature has extremely limited studies that address driving ability of CMV drivers while using licit Schedule II drugs. Because of this, the panel concluded that studies demonstrating impairments on indirect measures of driving ability following administration of Schedule II drugs should be given careful consideration even if the impairment was demonstrated in individuals who are not typical of CMV drivers.

Evidence Report Findings

Schedule II Opioids–single dose

2. **A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether first time administration of a Schedule II opioid has a deleterious effect on driving ability.**
   A single small, low quality study evaluated the effects of a single 50 milligram (mg) oral dose of codeine on driving ability as measured using a driving simulator in opioid naive healthy individuals. This study found that codeine had a significant deleterious effect on driving ability. Because this study is not of high quality and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

3. **First time administration of a single therapeutic dose of a Schedule II opioid to opioid-naive individuals has a deleterious effect on psychomotor and cognitive function. (Strength of Evidence: Moderate).**

   Six small, but otherwise high-quality studies assessed the effects of the administration of an opioid on some measures of cognitive (high level) and psychomotor function among opioid-naive healthy individuals. Four of the six

studies found that psychomotor and high-level cognitive function were adversely affected by a single dose of an opioid (morphine, alfentanil, meperidine, or fentanyl). The remaining two studies, both of which evaluated the effects of a single dose of codeine (30 to 100 mg), found no such drug effect. Whether this inconsistency in the findings of the six studies included in this assessment is a consequence of differences in the drugs themselves in drug dosage, in measurement timing, in the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

4. **A paucity of data meeting the inclusion criteria precludes one from determining whether first-time administration of an opioid has a detrimental effect on mood or behavior.**

   No included studies evaluated the effects of opioid on mood or behavior in opioid-naive individuals.

Expert Panel Statement

The expert panel felt that a paucity of data meeting the inclusion criteria precluded it from drawing an evidence-based conclusion regarding whether there is a relationship between the licit use of a Schedule II drug and motor vehicle (any category) crash risk. Panel members noted the absence of studies meeting the inclusion criteria and indicating impairment did not establish impairment. Members of the panel concluded that the existence of some studies demonstrating impairments in psychomotor and cognitive functioning following acute administration of Schedule II opioids was of enough concern that the current exception, which allows Schedule II drug use with proper prescribing physician documentation that the medication does not impair the individual's driving safety, should be eliminated. This recommendation will be discussed further in the section that follows.

Evidence Report Findings

Schedule II Opioids–Chronic Stable Use

5. **A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion pertaining to whether chronic (>7days) use of a Schedule II opioid has a deleterious impact on cognitive or psychomotor function at the present time.**

   Five low-quality studies assessed the effects of the long-term administration of an opioid on cognitive and psychomotor function among individuals with chronic pain. Four of them did not observe any detrimental effects of opioids on cognitive or psychomotor function. Two studies, however, provide some limited evidence in support of the contention that the long-term use of Schedule II opioids (transdermal fentanyl and controlled release morphine) may have a deleterious impact on cognitive and psychomotor function.

   The reader should note that none of the studies included in the evidence base considered here were designed as non-inferiority or equivalency studies. That is,

they were not designed to test the hypothesis that the administration of therapeutic doses of opioid does not have a deleterious impact on outcome. Rather, the included studies were designed to test the hypothesis that the administration of an opioid will have a deleterious impact on outcome. Failure to disprove the null hypothesis (not observing a treatment effect) by studies that utilize this design cannot be construed as providing evidence of no drug effect. Evidence from such studies, even when consistently observed by several independent studies, can, at best be considered as being suggestive of no treatment effect.

6. **A paucity of data meeting the inclusion criteria precludes one from concluding that stable (no change in dose in previous 7 days) therapeutic doses of a Schedule II opioid (morphine) has a detrimental effect on mood or behavior (Strength of Evidence: Weak).**

   Two small, low-quality studies meeting the inclusion criteria examined the effects of an opioid on mood and/or behavior among individuals with chronic pain. Neither study provided any evidence to support the contention that long-term use of morphine for a licit purpose has a negative impact on mood or behavior.

   As was the case above, the reader should note that neither included study was designed as a non-inferiority or equivalency study. Consequently, the finding of no evidence of a deleterious effect cannot be interpreted as providing evidence of no effect.

Expert Panel Statement

Panel members acknowledge that the studies meeting the inclusion criteria do not satisfactorily answer the question of whether licit, long-term use of Schedule II drugs negatively affects cognitive or psychomotor function, mood, or behavior. However, two of the studies did show negative effects on psychomotor and cognitive function. In addition, none of the studies examined the effect of these drugs in individuals with multiple chronic conditions, on multiple medications, or under the work stresses typical for CMV drivers. The included studies did not mimic a typical clinical situation in terms of additional short-term medications and did not observe the individuals over periods longer than two weeks. Furthermore, none of the included studies underpinning this conclusion (and the next) were designed as non-inferiority or equivalency studies. Rather, the included studies were designed to test the hypothesis that the administration of an opioid will have a deleterious impact on outcome. Failure to disprove the null hypothesis (not observing a treatment effect) by studies that utilize this design should not be construed as providing proof of no drug effect. The panel members stated the opinion that opioid therapy does impact cognitive and psychomotor function as well as mood and behavior.

In addition, the panel raised significant concerns about several issues relevant to the chronic use of Schedule II opioids not addressed in the available studies:

- The medical condition for which the Schedule II opioid is prescribed may be a sufficient reason for disqualifying an applicant.
- Pain management is “dynamic” – i.e., for most conditions,

  - The drug or dosage must be periodically changed; hence, therapy is not truly "stable."
  - Long-acting medications are often supplemented with short-acting medications for "breakthrough" pain (sometimes including Schedule III agents), which may cause important fluctuations in drug levels and effects.
  - Adjuvant pharmacotherapies (e.g., other pain-modulating agents, antidepressants, sedative hypnotics and antianxiety drugs) prescribed in the setting of chronic pain may also be changed and/or dosages adjusted, and may interact with the Schedule II opioid, altering the individual's ability to drive at any given dose of the opioid.

- The demands placed on CMV drivers in their work environment complicate adherence to prescribed dosing intervals and precautions. Factors such as irregular meal timing, periods of sleep deprivation or poor sleep quality, as well as irregular or extended work hours were specifically noted as potentially modulating drug effects and leading to missed doses or erratic dosing. In addition, physical demands of CMV operation such as loading and unloading, or working with load securement devices may exacerbate the underlying painful condition, necessitating additional supplemental medication for breakthrough pain.
- The medical examiner is at risk in allowing an individual to operate a CMV while taking Schedule II drugs because, if the driver crashes, the crash will be attributed to drug use and the medical examiner's decision to qualify the driver using a prescribed Schedule II medication to operate a CMV may be questioned.

Panel members again strongly recommended elimination of the current exception allowing the individual to operate a CMV even if the treating physician provides a written statement that the Schedule II opioid medication does not impair the individual's driving safety. Furthermore, the panel unanimously stated that no exceptions should be granted for Schedule II opioids. Reasons for this recommendation include the following:

- There is currently a virtual epidemic of abuse of Schedule II opioids in the United States, obtained both legally and illegally.
- There is at least some data suggesting an increase in risk of impairment with Schedule II opioids.
- Most treating physicians do not have sufficient understanding of the specific work demands on the CMV driver, the potential risks to public safety and the relevant regulations and guidance.
- Treating physicians primarily represent their patients' interests, rather than the interests of the employer and/or the general public. This affects their subjective assessment of whether the individual taking a Schedule II medication will be able to drive a CMV safely.
- Logistical difficulties in obtaining records and time pressures to complete the medical report form complicate the medical examiner's ability to assess the appropriateness of the prescribing physician's statement.

- Given the spectrum of licensed health care professionals currently permitted by statute to perform medical examinations for CMV drivers, the panel expressed concern that many examiners would not have sufficient knowledge of the effects of Schedule II drugs on an individual's ability to perform CMV operations, the regulations and the available FMCSA guidance. In addition, the medical examiner may not fully understand the pharmacology of the Schedule II agents or the conditions being treated with Schedule II drugs. This lack of knowledge would severely limit the ability of the examiner to adequately assess the prescribing physician's statement and documentation. Once the National Registry and certification is implemented, the panel recommends reevaluation of this issue.
- Several members of the panel raised concerns about the exclusion of data from studies in which indirect measures of driving ability were reported for groups of individuals, some of whom were taking Schedule II opioids for chronic pain under medical supervision, and some of whom were illicitly using Schedule II drugs.

The panel had extensive discussion in recommending the elimination of the exception for Schedule II opioids, especially when discussing intermittent use. Part of the issue was in the definition of intermittent use. The panel believed that intermittent, appropriately prescribed use of Schedule II pain medications for acute conditions could be permitted provided the driver has not taken that medication for at least twice the recommended dosing interval prior to operating a CMV. This understanding would need to be carefully understood by driver and treating health care professionals (who should also be aware of any other medications that driver might be taking) and the carrier. This recommendation is consistent with the National Transportation Safety Board recommendation I-00-3 (January 13, 2000).

Evidence Report Findings

Findings Specific to Licit Schedule II Stimulant Use

7. **A paucity of data meeting inclusion criteria precludes one from determining whether the licit long-term use of a Schedule II stimulant for the treatment of a legitimate medical condition has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior such that the risk for a motor vehicle crash is increased.**
   No included studies evaluated the effects of the long term licit use of a stimulant on any of the outcomes relevant to Key Question 2.

8. **A paucity of data meeting inclusion criteria precludes one from determining whether the administration of therapeutic doses of a Schedule II stimulant to stimulant-naive individuals has a detrimental impact on driving ability.**

   Two high quality studies assessed the effects of Schedule II stimulants (dextroamphetamine and methylphenidate) on simulated driving ability. The findings of these two studies were not consistent. One included study did not observe any deleterious effects on simulated driving ability associated with methylphenidate (10 mg or 20 mg) when given to individuals with attention deficity hyperactivity disorder (ADHD. The other study found that a single dose of

dexamphetamine (0.42 mg/kg) has a deleterious impact on daytime (but not nighttime) simulated driving in the stimulant-naive healthy individual. Whether the differences in the qualitative findings of the two studies is the consequence of differences in the drugs tested, in drug dosage, in measurement timing, in the sensitivity of the driving simulators used to evaluate driving ability, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

9. **The best-available evidence does not support the contention that the administration of a single therapeutic dose of a Schedule II stimulant to a stimulant-naive individual will have a deleterious impact on cognitive and/or psychomotor function (Strength of Evidence: Weak).**

   Five moderate-to-high quality studies presented data on the acute effects of stimulants on cognitive and/or psychomotor function. None of these studies found that the administration of a therapeutic dose of a Schedule II stimulant had a deleterious impact on cognitive or psychomotor function.

   Despite the fact that the overall quality of the evidence base underpinning this conclusion was high and the data from all five studies are qualitatively consistent and robust, we refrain from assigning a "Strength of Evidence" rating of "Strong" to this conclusion. This is because none of the included studies were non-inferiority or equivalency studies (see the previous discussion above).

10. **The best-available evidence does not support the contention that the administration of a single therapeutic dose of a Schedule II stimulant to a stimulant-naive individual will have a deleterious impact on domains of mood and/or behavior that are likely to increase the risk for a motor vehicle crash (Strength of Evidence: Weak).**

    Three high quality studies presented data on the effects of a single dose of a stimulant on mood and/or behavior. None of the studies found that stimulants had a deleterious effect on mood or behavior. In fact, data from the three studies suggests that the some of the effects of the stimulants on mood and behavior were positive (improved focus, etc).

    Despite the fact that the studies from which these data originated were of high quality, the findings should be viewed with caution. This is because mood and behavior data from two of the three included studies were based on test subject self-perception. An individual's internal perception of their own behavior while under the influence of a drug cannot be considered as a good indicator of their actual demeanor. Data from the third study is equally suspect since it was based on a rather informal description of the behavior of the test subjects. To reflect our concern about the potential mischaracterizations of the true mood and behavior states of the individuals enrolled in the included studies, we have downgraded the strength-of-evidence rating from high to weak.

Expert Panel Statement

A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether there is a relationship between the licit use of a Schedule II drug and motor vehicle (any category) crash risk. Short-term Schedule II stimulant use is not consistent with Federal Drug Administration- (FDA) approved indications. Long-term use, particularly for attention deficit disorder (ADD) or ADHD, should be further considered by experts on these medical conditions. The panel strongly recommended that exceptions for CMV drivers taking Schedule II stimulants only be granted when prescribed for ADD/ADHD that has been appropriately evaluated and diagnosed. The panel urged careful consideration as to whether the underlying conditions themselves should be grounds for disqualifying applicants. The panel recommends that FMCSA provide guidance to medical examiners regarding appropriate documentation from treating physicians. In addition, they recommend the development and use of standardized forms for communication between the treating physician and medical examiner which make clear that in signing the form, the treating physician's primary obligation is to ensure public safety.

Evidence Report Findings

Findings Specific to Licit Schedule II Depressant Use

11. **A paucity of data meeting inclusion criteria precludes one from determining whether the licit long-term use of a Schedule II depressant has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior such that the risk for a motor vehicle crash is increased.**

    No included studies evaluated the effects of the long term licit use of a Schedule II depressant on any of the outcomes relevant to Key Question 2.

12. **A paucity of data meeting inclusion criteria precludes one from drawing an evidence-based conclusion pertaining to whether the administration of therapeutic doses of a Schedule II depressant to depressant-naive individuals has a detrimental impact on driving ability.**

    One included moderate quality study evaluated the effects of repeated doses (five doses over 36 hours) of a Schedule II depressant (amylobarbitone) on driving ability as measured by a series of low speed vehicle handling tests. Test subjects were all normal healthy individuals. The results of the study suggest that a therapeutic dose of amylobarbitone, when taken over the preceding 36 hour period by healthy individuals, does have a detrimental impact on driving ability. Because this study is not of high quality and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

13. **Therapeutic doses of a Schedule II depressant appear to have a deleterious impact on cognitive and psychomotor function (Strength of Evidence: Weak).**

    Two moderate-quality studies consistently found that cognitive and psychomotor function was impaired following the administration of a single dose of Schedule II depressanst (secobarbital and pentobarbital). Whether the results of these two

studies can be generalized to other depressants in the same class (barbiturates) cannot be determined.

14. **A paucity of consistent data from high-quality trials precludes one from drawing an evidence-based conclusion about whether the deleterious effects of Schedule II depressants continue to effect performance the morning after administration of a therapeutic dose.**

    Because one of the primary medical indications for a Schedule II depressant is insomnia, it is important to determine whether the adverse effects that the drugs have on cognitive and psychomotor function can be observed the morning after their administration.

    Three studies evaluated the effects of a single dose of barbiturate the morning after its administration. The results of these studies were not consistent with one another. One moderate quality study did not find any evidence of reduced cognitive or psychomotor function the morning after administration of a single 100 mg dose of amylobarbitone. However, the remaining two studies (one administered a single 200 mg dose of amylobarbitone and the other administered a single 200 mg dose of secobarbital/amobarbital mix) found that cognitive and psychomotor function were impaired the day after administration of the drug. Whether this inconsistency in the findings of the three included studies is a consequence of differences in drug dosage, in the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

15. **A paucity of data precludes one from drawing an evidence-based conclusion pertaining to whether the chronic administration of therapeutic doses of a Schedule II depressant has a detrimental impact on cognitive and psychomotor function.**

    A single high-quality study evaluated the effects of 7 days of Schedule II depressant (amylobarbitone) administration on cognitive and psychomotor function. This study enrolled individuals with a clinical diagnosis of anxiety neurosis who had been admitted to a hospital for crisis intervention. The study found that chronic high therapeutic doses of amylobarbitone (463 mg/day) had a deleterious effect on cognitive and psychomotor function. Of the nine relevant outcomes measured, two were significantly impaired. Whether these findings are the consequence of chance or are representative of a true drug effect is not clear. Replication studies performed with different patient populations and Schedule II depressants are required before evidence-based conclusions about the effects of long-term Schedule II depressant treatment can be drawn.

16. **Administration of therapeutic doses to Schedule II depressant-naive individuals does not appear to have a deleterious impact on mood or behavior that might be considered detrimental to motor vehicle safety (Strength of Evidence: Weak).**

    Two high-quality studies evaluated the effects of a Schedule II depressant on mood and behavior. Neither study detected any adverse effects of the drugs on either outcome.

Expert Panel Statement

A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether there is a relationship between the licit use of a Schedule II drug and motor vehicle (any category) crash risk. Panel members were unanimous in recommending that no exceptions should be granted for use of Schedule II depressants by CMV drivers because of a paucity of data meeting inclusion criteria. Some of the available data does in fact show impairment. Panelists strongly urged FMCSA to proceed with an examination of the risk of use of all sedative, hypnotic, antianxiety, antidepressant and any other psychoactive medications, regardless of DEA Schedule. Panel members stated that benzodiazepines are of particular importance given the frequency with which they are prescribed and studies in the medical literature associating use of these drugs with increased risk of motor vehicle crashes.

Key Question #3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Evidence Report Findings

1. **A paucity of data meeting inclusion criteria precludes one from drawing any conclusions concerning the relationship between the serum level of a Schedule II drug and motor vehicle (any category) crash risk.**

   Although we retrieved 49 potentially relevant articles that described 49 unique studies, none was found to report on the relationship between the serum level of a Schedule II drug and motor vehicle crash risk. Consequently no evidence base currently exists with which one can answer this question.

Expert Panel Statement

The panel did not comment on Key Question 3. The panel questions the applicability of this question to the process of CMV medical qualification.

Key Question #4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?

Evidence Report Findings

1. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between serum levels of Schedule II stimulants and depressants and any of the outcomes of interest (driving ability, cognitive and/or psychomotor function, and mood and behavior).**

   No study meeting the inclusion criteria for Key Question 4 evaluated a Schedule II stimulant or depressant.

2. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between serum levels of Schedule II opioids and driving ability or mood and behavior.**

No study meeting the inclusion criteria for Key Question 4 investigated the relationship between the serum level of a Schedule II opioid and driving ability or mood and behavior.

3. **The magnitude of the acute cognitive and psychomotor functional deficits observed among opioid-naïve individuals following administration of a single dose of Schedule II opioid are correlated with the serum level of the drug (Strength of Evidence: Strong).**

   Three moderate to high quality studies observed a relationship between serum levels of a Schedule II opioid (morphine) and some (but not all) measures of cognitive and/or psychomotor dysfunction. The measures that demonstrated the strongest relationship with drug serum level tended to be measures of higher order functioning.

4. **Measures of high level cognitive and psychomotor function are inversely correlated with the serum level of Schedule II opioids (Strength of Evidence: Weak).**

   Two low quality studies observed significant correlations between serum levels of Schedule II opioids (fentanyl and morphine) and a number of high level measures of cognitive and/or psychomotor function.

Expert Panel Statement

The Expert Panel believed that a paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether there is a relationship between the serum level of a Schedule II drug and indirect measures of driving ability**.** Panel members did not see any general role for drug level measurement in the process of assessing the safety of Schedule II drug use. However, the studies demonstrating a relationship between drug levels and impairment reinforce their concerns about the safety of long-term Schedule II opioid use.

Key Question #5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

Evidence Report Findings

1. **A paucity of data meeting inclusion criteria preclude one from drawing conclusions concerning the relationship between Schedule II drug pharmacokinetics and motor vehicle (any category) crash risk.**

   Although we retrieved 11 potentially relevant articles that described 11 unique studies, none provided direct evidence pertaining to the relationship between crash risk and Schedule II drug pharmacokinetics. Consequently no evidence base currently exists with which one can answer this question.

Expert Panel Statement

The panel did not comment on Key Question 5.

Key Question #6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

Evidence Report Findings

1. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of Schedule II drugs and driving ability (as measured by a simulator or on a prespecified driving course).**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this outcome.

2. **The pharmacokinetics of Schedule II opioids (morphine, fentanyl, and meperidine) are closely correlated with temporal changes in measures of cognitive and psychomotor function in healthy opioid-naïve individuals (Strength of Evidence: Strong)**

   Three included studies demonstrated the existence of the relationship between the pharmacokinetics of Schedule II opioids (morphine, fentanyl, and meperidine) and temporal changes in measures of cognitive and psychomotor function.

3. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of a Schedule II opioid and temporal changes in measures of cognitive and psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of opioids.

Expert Panel Statement

The Expert Panel believed that a paucity of data meeting the inclusion criteria precluded it from drawing an evidence-based conclusion regarding the relationship between the pharmacokinetics of Schedule II opioids and driving ability (as measured by a simulator or on a prespecified driving course). Panel members acknowledged that opioids differ in their pharmacokinetic profiles. The demonstration of a relationship between pharmacokinetic properties of morphine, fentanyl, and meperidine and temporal changes in cognitive and psychomotor function reinforced the panel's opinion that no exceptions should be granted for Schedule II opioids. Panel members cautioned that the **paucity of data meeting the inclusion criteria** regarding such a relationship for other Schedule II opioid drugs does not constitute evidence that these other drugs are safe.

Evidence Report Findings

4. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of Schedule II stimulants and temporal changes in measures of cognitive and psychomotor function in healthy stimulant-naïve individuals.**

A single included study investigated the relationship between the pharmacokinetics of a Schedule II stimulant (dextroamphetamine) and temporal changes in cognitive and psychomotor function in healthy stimulant-naïve individuals. This small, but otherwise high quality study demonstrated a temporal relationship between dextroamphetamine concentration and cognitive function. Because of the small size of the study, replication is required before evidence-based conclusions can be drawn.

5. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of a Schedule II stimulant and temporal changes in measures of cognitive and psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of stimulants.

Expert Panel Statement

The Expert Panel believed that a paucity of data meeting the inclusion criteria precluded it from drawing evidence based conclusions about the relationship between the pharmacokinetics of a Schedule II stimulant and temporal changes in measures of cognitive and psychomotor function in healthy stimulant-naïve individuals or chronic licit users of the drugs. Panel members cautioned that the **paucity of data meeting the inclusion criteria** regarding a relationship between the pharmacokinetic properties of Schedule II stimulants and temporal changes in measures of cognitive and psychomotor performance does not constitute evidence that there is no relationship. Panel members expressed concern that withdrawal from the effects of stimulants may make an individual more impaired than while under the therapeutic effects.

Evidence Report Findings

6. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of Schedule II depressants and temporal changes in measures of cognitive and psychomotor function.**

   No studies of Schedule II depressants met the inclusion criteria for Key Question 6.

Expert Panel Statement

Panel members cautioned that the **paucity of data meeting the inclusion criteria** and addressing the relationship between the pharmacokinetic properties of Schedule II depressants and temporal changes in indirect measures of driving ability does not constitute evidence that there is no relationship.

Evidence Report Findings

7. **A paucity of data meeting inclusion criteria precludes one from drawing conclusions about the relationship between the pharmacokinetics of Schedule II drugs and temporal changes in mood or behavior.**

No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this outcome.

Expert Panel Statement

Panel members noted that the **paucity of data meeting the inclusion criteria** regarding a relationship between the pharmacokinetic properties of Schedule II stimulants and mood and behavior does not constitute evidence that there is no relationship.

Key Question #7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

Evidence Report Findings

1. **No conclusions from direct evidence concerning the relationship between the serum level of a Schedule II drug and motor vehicle (any category) crash risk can be drawn at the present time.**

   Although our searches identified 14 potentially relevant articles, none were found to meet the retrieval criteria. Consequently, no evidence base currently exists with which one can answer this question.

Expert Panel Statement

A paucity of data meeting the inclusion criteria precludes one from drawing an evidence-based conclusion regarding whether there is a relationship between drug interactions with prescribed Schedule II drug use and motor vehicle (any category) crash risk.

Key Question #8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

Evidence Report Findings

1. **A paucity of data precludes one from drawing evidence based conclusions pertaining to the effect of combining a Schedule II drug with another drug on driving ability, cognitive or psychomotor function, and mood and behavior.**

   Four relevant studies met the inclusion criteria for this report. Each study evaluated the effects of a different combination of a Schedule II drug with another drug. Because none of the studies were high-quality mega-trials, replication is required before evidence based conclusions about the effects of combining Schedule II drugs with other drugs can be drawn.

Expert Panel Statement

Panel members acknowledge that medical literature offers scant information about the effect of licit use of multiple Schedule II drugs on CMV driving ability. Panel members also concluded that Schedule II opioids ***and depressants*** should not be used by CMV

drivers regardless of concomitant medications or underlying medical conditions present. Panel members recommended continued monitoring of the medical literature to identify high-risk combinations of drugs, particularly with Schedule II stimulants.

Expert Panel Conclusions

The panel concluded that the MRB and FMCSA should strongly consider removing the current exception in CFR 391.41 (b)(12)(ii) for Schedule II opioids and depressants and that additional requirements be included in the standard for use of Schedule II stimulants in ADD/ADHD. The panel recommends further study of an expanded list of controlled substances such as Schedules III and IV opioids and benzodiazepines. The panel also urged study of risks associated with over-the-counter medications.

Other recommendations for future consideration were:

- Because of the strict inclusion criteria, the scientific review excluded many studies the panel felt were relevant. Additional and broader review of the scientific literature on Schedule II drugs and crash risk, including case reports, impairment related to illicit use of these drugs, impairment studies not limited to driving, etc., should be included in any further evaluation of the scientific literature regarding impairment.
- Enhanced post-accident procedures to evaluate the effect of medications on crash risk.
- Expansion of the panel of drugs for which tests are performed beyond the current five permitted by federal regulations.
- Creation of a mechanism for evaluating individuals after treatment for substance abuse not identified by federally permitted drug testing. Follow-up testing in such CMV drivers should be considered.
- Expansion of safety education for carriers and drivers on risks associated with prohibited drug use.
- Improvement of guidance and consideration of required reporting for the medical review officer finding positive drug tests in CMV drivers.
- Better definition of “current” valid prescription use by CMV drivers.
- Improved guidance provided by the FMCSA to medical examiners regarding appropriate documentation from treating physicians for permitted medication use.
- Standardized forms provided by the FMCSA to be used for clarification of medical conditions and prescribed medications.
- Another look at the prohibition of Schedule II opioid use after the medical examination process has been modified to include the National Registry program. FMCSA should provide detailed guidance for evaluation criteria for use of Schedule II opioids, as well as standardized forms within the required training. In challenging cases such as with Schedule II opioids, a medical review process that can address individual cases would be ideal.