Evaluating Drug Effects on the Ability to Operate a Motor Vehicle

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Contains Nonbinding Recommendations

Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist pharmaceutical sponsors in the evaluation of the effects of psychoactive drugs on the ability to operate a motor vehicle. Specifically, this guidance addresses the FDA's current thinking regarding FDA-regulated drugs for which such evaluation may be needed[2] and the types of studies that such an evaluation entails during clinical trials.

This guidance does not address the specific methods or instruments used to collect data on driving ability; rather, this guidance outlines the general principles and goals of such studies. Experience suggests that a number of methods may be suitable for providing the necessary data. For specific drug development programs, sponsors should discuss with the appropriate review division the study methods to be used.

This guidance also does not address the effects on driving ability from underlying disease, normal aging, or other factors unrelated to regulated drugs (e.g., distracted driving, aggressive driving). Although psychoactive drugs are the focus of this guidance, nonpsychoactive drugs may affect driving ability through effects on function, including intended effects and secondary effects (e.g., impaired consciousness from a hypoglycemic reaction to a glucose-lowering drug, impaired vision from a mydriatic drug). Therefore, the need to consider possible effects on driving ability is not limited to psychoactive drugs, and the approach to evaluating risk for nonpsychoactive drugs, which may differ substantially from the approaches described in this guidance, should be guided by drug-specific effects.

[1] This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Driving is a complex activity involving a wide range of cognitive, perceptual, and motor activities. Reducing the incidence of motor vehicle accidents (MVAs) that occur because of drug-impaired driving is a public health priority. A systematic effort to identify drugs that increase the risk of MVAs is a critical component of assessing drug risk and designing strategies to reduce this risk.

Drugs that impair driving ability may also impair an individual's ability to judge the extent of his or her impairment. Therefore, in general, patient self-perception is not adequate for evaluating the presence or degree of driving impairment or for mitigating risk. Instead, objective information about how a drug affects driving ability may be needed to enable safe use.

III. THE NEED TO EVALUATE DRIVING IMPAIRMENT

When determining whether to evaluate the effect of a drug on driving ability, sponsors should first consider the conditions for use of the drug and the intended patient populations. Drugs intended for chronic (including chronic-intermittent) outpatient use by adults are most likely to need evaluation of effects on driving ability. In contrast, drugs limited to use in young children or to use in hospital inpatient settings would not need such evaluation. FDA recommends that sponsors engage in early discussions with the appropriate review division to determine whether studies are needed in any given development program to evaluate drug effects on driving ability.

Drugs that have pronounced central nervous system (CNS) impairing effects and are intended to be administered primarily at night (e.g., drugs for insomnia and other sleep disorders) are of concern because residual daytime effects can impair driving ability.

In some cases, psychoactive drugs may appear to have the potential to *improve* driving performance, for example by decreasing somnolence (an established risk factor in MVAs). However, such drugs can have additional effects that increase the likelihood of driving impairment; for example, CNS stimulants may increase risk-taking (e.g., aggressive driving). Consequently, sponsors of psychoactive drugs should consider additional data on other functions important for safe driving.

Sponsors also may need to conduct driving studies if an active moiety approved for a particular use is proposed for a different indication, at a different dose or dosing schedule, or in a new patient population in which there is insufficient information about how the drug may affect driving ability. For example, drugs with well-known CNS depressant activity, such as

barbiturates and benzodiazepines, have been used in wide ranges of doses and schedules for a number of indications, from anxiety to insomnia to general anesthesia. Potential effects on driving ability may differ among the various uses and patient populations.

The driving impairment studies described in this guidance may be impossible to conduct in the intended patient population or may need modification for drugs associated with serious safety risks that prevent enrollment of healthy subjects. Depending on the specific circumstances, the risk of driving impairment might be adequately addressed using data that were feasible to collect combined with labeling that addresses remaining uncertainty. Sponsors should discuss such approaches with the relevant review division during drug development.

IV. TIERED APPROACH TO EVALUATING DRUG EFFECTS ON DRIVING ABILITY

A drug's effect on driving ability cannot be assessed using the risk of actual MVAs because using MVAs as endpoints in randomized controlled trials would be unethical. Instead, sponsors should use studies that assess the effects of a drug on CNS functions necessary for safe driving and, if necessary, driving tests to determine the potential for causing MVAs.

The FDA recommends evaluating impaired driving using a *tiered assessment*[3] consisting of pharmacology/toxicology, epidemiology, and clinical/standardized behavioral assessments. With this approach, sponsors can use drug information obtained early in development to guide the need to collect data later in development related to driving impairment potential. This can ensure that resources are not unnecessarily expended on evaluating drugs with little to no potential for impairment or on tests of drugs that are so clearly impairing when used as indicated that a detailed study is unnecessary (e.g., drugs used for surgical anesthesia). Early in drug development, assessments should have high sensitivity for detecting impairment. Later in development, studies should be designed to characterize the clinical relevance of earlier findings. The following broad functional domains are important for driving ability and should be assessed with increasingly focused studies if accumulating data suggest a risk of clinically meaningful driving impairment:

- Alertness/arousal/wakefulness
- Attention and processing speed
- Reaction time/psychomotor functions
- Sensory-perceptual functioning
- Executive functions

[3] Kay, GG and BK Logan, 2011, Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving, DOT HS 811 438, Washington, DC: National Highway Traffic Safety Administration.

A. Pharmacology/Toxicology

The chemical structure or receptor binding profile of a drug can suggest the potential to affect driving ability. For example, drugs with a benzodiazepine structure or that promote binding of gamma-aminobutyric acid to the drug's receptors are likely to have CNS depressant effects and will need close attention to depressant effects in clinical trials. However, structure and receptor binding alone may not be sufficient to conclude that a drug does *not* impair driving ability because cortical functions such as judgment are not well assessed in structure/binding studies. Similarly, the primary mechanism of action may not be adequate to provide reassurance about safety because unanticipated off-target actions can cause adverse effects.

The pharmacokinetic properties of a drug can be critical for evaluating the driving impairment risk that a drug may cause. Plasma or, if more relevant, brain tissue half-life is particularly important for drugs when the patient is expected to be active at night or at other times when the patient is typically not expected to be driving. Another important factor may be the extent of blood-brain barrier penetration, as illustrated by differences in somnolence caused by first- versus second-generation H_1 antihistamines related in part to differences in blood-brain barrier penetration.

Nonclinical studies may provide data useful for anticipating the potential for a drug to impair driving ability. In general, nonclinical studies for evaluating potential for impaired behavior should include an in vitro binding panel to assess on- or off-target pharmacologic targets of the drug, assays to assess the pharmacologic activity at the targets, and an in vivo CNS safety pharmacology study with careful assessment of signs potentially indicative of impaired CNS function. Sponsors should consider the pharmacological activity and pharmacokinetics of major circulating metabolites in humans, as well as the effect of the parent compound.

B. Use of Epidemiological Data

Evidence from drugs of the same or similar class, or with similar activity profiles, may raise concern about the effects of a drug on driving ability. Epidemiological data can also be useful for understanding how various factors related to actual clinical use (e.g., drug-disease interactions, drug-drug interactions, dosing errors) may impact the effect of a new drug on driving ability.

Epidemiological data may show an association between a specific illness (e.g., narcolepsy, obstructive sleep apnea) or a driver subset (e.g., young men) and an increased risk for MVA.[4] Although the focus of this guidance is limited to drug effects on driving ability, taking epidemiological information about possible vulnerability to drug problems into consideration may be important when designing or interpreting driving studies.

Epidemiological data, however, are generally poorly suited to provide convincing evidence that a drug or drug class does or does *not* increase the risk of MVAs. MVAs are common, and even in

[4] LeRoy, AA and ML Morse, 2008, Multiple Medications and Vehicle Crashes: Analysis of Databases, DOT HS 810-858, Washington, DC: National Highway Traffic Safety Administration.

patients with clinically meaningful impairment, many other factors contribute to the occurrence of a collision, decreasing the power of epidemiological studies to reliably identify increased risk from drug use, which is at worst only one factor among many increasing risks. Patient population and other disease-specific factors can also have a large effect on MVA risk.

Similarly, postmarketing adverse event reports are of limited use for identifying drugs that do or do not impair driving ability. First, there is limited ability to verify critical circumstances of use such as dose, timing, and concomitant use of other drugs or alcohol. In addition, the high background rate of MVAs and the recognized relation of MVAs to age, sex, driving experience, and many other factors are poorly documented in spontaneous reports. Finally, underreporting may occur if patients and providers are not aware that impairment from a drug may have contributed to an MVA.

C. Clinical/Behavioral Asessment

1. Phase 1 Drug Development Trials

Beginning with first-in-human trials, all drugs, including drugs intended for non-CNS indications, should be evaluated for adverse effects on the CNS (e.g., somnolence, agitation, dizziness). The occurrence of concerning adverse CNS events at clinically relevant exposures in even a small number of phase 1 subjects might indicate the need for more focused studies of CNS-impairing effects. However, if few adverse events are observed for a drug with no biologic plausibility of CNS effects, additional studies may not be warranted.

Early testing for CNS-impairing effects should generally emphasize sensitivity over specificity. Psychomotor and neuropsychological tests, including measures of reaction time, divided attention, selective attention, and memory may be appropriate. Early trials often include higher doses than will be used in later efficacy trials, which provides an opportunity to explore CNS-impairing effects at higher exposures. For drugs designed to affect sleep and wakefulness, directed studies such as the multiple sleep latency test or maintenance of wakefulness test may help to inform about both drug safety and efficacy. Subjective evaluation of CNS-impairing effects (e.g., by visual analogue scale) can contribute important information with respect to the strength of the correlation between subjective and objective impairment.

If there is initial evidence of impairing effects, additional studies should examine CNS impairment over the full range of drug exposures that may occur in phase 2 and 3 trials. Studies should include consideration of active metabolites and increased exposure in subpopulations such as those with genetic polymorphisms that lead to decreased levels of metabolizing enzymes or those with renal or hepatic insufficiency.

In studies primarily intended to examine CNS impairment, a positive control is critical for study interpretability. In general, negative studies in the absence of demonstrated assay sensitivity are not interpretable. Even for studies that show impairment, a positive control is useful to understand the magnitude and duration of impairment. Commonly used positive controls include ethanol, sedating antihistamines, and benzodiazepine-like drugs. Other positive controls may be appropriate and should be discussed with the FDA.

2. Phase 2 and 3 Trials

For drugs with potential effects on driving ability (e.g., drugs with sedating properties, drugs in early testing suspected of impairing CNS functions necessary for driving), it is particularly important that drug blood levels, including major active metabolites, should be measured during phase 2 and 3 trials. Sponsors should document factors that affect blood levels, such as time of dosing, food effects, and concomitant treatments (see IV. C.1., Phase I Drug Development Trials). The number and timing of blood concentration measurements should be adequate to support examination of exposure-response relationships. We recommend that sponsors share and discuss with the appropriate review division analysis plans to explore relationships between drug and active metabolite concentrations and potential effects on driving ability to confirm the adequacy of the analyses.

For drugs identified in early development as having a high potential to cause impairment, patients should be monitored at appropriate intervals during phase 2 and 3 trials for signs and symptoms that could place individuals at unacceptable risk. While this monitoring should be guided by adverse effects elicited in earlier-phase testing (e.g., somnolence, dizziness, depressed level of consciousness, disturbance in attention, hypersomnia, lethargy, mental impairment, stupor, altered state of consciousness, and drugged feeling), monitoring should be broad enough, as discussed below, to detect effects that might not have been previously identified, such as impaired executive function or memory (e.g., amnesia, memory impairment, retrograde amnesia, amnestic disorder, global amnesia).

Investigators should use both open-ended and targeted questions regarding adverse effects. Specific patient-reported outcomes that measure relevant symptoms, such as sleepiness scales, can help to quantify severity. Investigators should ask patients (and family members when appropriate) about their perceived driving ability; negative responses provide limited reassurance of safety, but positive reports of difficulty staying awake while driving or collision near misses are informative. Sponsors should specifically query patients about the occurrence of CNS symptoms such as inattention, sleepiness, and impaired judgement experienced while driving. In studies during phase 2 and 3 trials, sponsors should document to the degree possible the time of day and duration of adverse effects on the CNS because this information can characterize temporal effects on the risk of driving impairment.

Objective tests of psychomotor function, as described in section IV.C.1., Phase 1 Drug Development Trials, may also be needed to protect patient safety adequately. During phase 2 and 3 trials, sponsors should document to the degree possible the time of day and duration of adverse effects on the CNS because this information can characterize temporal effects on the risk of driving impairment. Sponsors should specifically query patients about the occurrence of adverse drug effects experienced while driving. The FDA encourages sponsors to collect data on actual MVAs and traffic violations in phase 3 trials, although such events are generally infrequent.

3. Driving Studies

If accumulating data suggest a potential for driving impairment, dedicated driving studies with higher specificity than more general tests of CNS function may be needed to refine assessment of the clinical effect of impairment. Sponsors can conduct such studies with either actual motor vehicles or driving simulators. Sponsors should consider the advantages and disadvantages of selected approaches and discuss any relevant issues with the appropriate review division. For instance, if the sponsor is conducting a driving study with a simulator, the sponsor should consider whether thresholds for impairment have been established and, if not, how to approach the establishment of a meaningful threshold.

Driving is a multifaceted activity and any given test of driving ability may not be capable of characterizing all of the different types of drug effects that can impair driving ability. For example, sustained ability to maintain driving lane position in a monotonous driving environment has been used to assess drug-related somnolence but may be substantially less informative with respect to executive functions, which may be better tested in driving scenarios presenting new or more demanding situations, such as those that might call for anticipatory adaptation of vehicle speed or go/no-go decisions. Sponsors should explain the rationale to support their selections of administered tests.

Sponsors should include positive control and placebo groups in dedicated driving studies. The positive control should be selected based on its ability to confirm assay sensitivity at the threshold of concern for clinically meaningful driving impairment. An important, but not the only, benchmark for sponsors to consider when selecting a positive control is the impairment caused by ethanol at various blood levels, including levels that are per se illegal for driving. An example of a positive control may be a drug that the FDA approved with detailed labeling regarding driving impairment.

Enrolling subjects in driving studies who are from the population likely to use the drug, including the elderly, is important for providing information about disease-drug interactions. In some cases, however, it might be possible to conclude that differences between healthy subjects and patients are sufficiently small to allow healthy subjects to be studied.

Generally, sponsors should conduct driving studies to evaluate both the effects of initial drug exposure and effects after chronic exposure. Drugs or active metabolites with a long half-life can result in markedly higher blood levels after multiple doses than occur after a single dose causing greater impairment with chronic, as compared to initial, use. Conversely, initial exposure to a drug may be more impairing than chronic exposure because there may be development of pharmacological tolerance or habituation over time. Testing of driving ability should take place when maximal levels of parent and/or active metabolite(s) are achieved. Even if tolerance develops, it is often incomplete and may only develop after an extended duration of exposure. Therefore, determining the time course and extent of any tolerance that develops can be important for instructing patients adequately about safe use.

Studies of driving impairment should include an assessment of drug effects at the highest relevant exposures expected to be encountered in clinical use. Therefore, sponsors should study

drug exposures at the highest therapeutic doses and possibly at doses above the intended therapeutic dose to account for increased levels in subsets of patients, such as patients taking concomitant medications that cause drug-drug interactions leading to higher blood levels or increased pharmacodynamic effects or patients with specific genetic traits or other characteristics (e.g., renal hepatic disease) that could lead to higher exposures.

For certain drugs intended to be dosed at night, including drugs for sleep disorders, effects on the CNS, which have an intended effect at night, *cannot* be assumed to be absent at the lower blood levels expected during the following day, especially in the morning. Focused studies of residual CNS-impairing effects may be needed to characterize the risk of driving impairment.

4. Randomization

A randomization scheme is described below for testing both the acute (1 dose) and later (1 week in this example) effects of a drug on driving ability.

The example design is a randomized, double-blind, double-dummy, placebo and active-controlled multiple oral dose, four-period crossover study. In treatment periods 1 through 4, subjects are randomized to receive the following treatments in a double-dummy fashion (with a well-matched placebo):

A. High dose test drug for 8 days
B. Low dose test drug for 8 days
C. Positive control, day 1 and day 8
D. Placebo

The investigational drug is given for 8 consecutive days to determine whether tolerance/desensitization develops; the finding of less impairment on day 8 than day 1 would indicate the development of tolerance. The positive control is given only on days 1 and 8 so that there is no opportunity for the development of tolerance that could confound interpretation of the study.

A minimum 5 half-life washout period occurs between each treatment dosing period for any given subject. Driving tests are conducted at both the beginning of each study period (after the first dose or few doses) and at the end of the study period.

Table 1 shows the treatment assignments for each period.

Table 1. Treatment Assignments

N	Period 1 (8 Days)	Washout	Period 2 (8 Days)	Washout	Period 3 (8 Days)	Washout	Period 4 (8 Days)
	A		C		D		B
	B		D		C		A
	C		B		A		D
	D		A		B		C

For drugs that have considerably long half-lives, parallel study design may need to be considered. Otherwise, if less than a 5 half-life washout period is proposed, sponsors should provide justification with discussion of whether a carry-over effect exists.

5. Endpoint Analysis

Although analysis of safety endpoints based on mean effect can be informative, exposure (e.g., maximum plasma concentration, area under the curve, tissue levels) from many drugs varies among subjects by an order of magnitude or more. Thus, clinically meaningful impairment in subjects at the high end of drug exposure may not be predicted by mean changes. Differences in pharmacodynamic sensitivity among subjects may also result in meaningful impairment in individual subjects that may not be predicted by aggregate measurements. Therefore, sponsors should examine the entire distribution of a measure of impairment, rather than just its mean, paying special attention to values that indicate clinically meaningful impairment.

6. Exposure-Response Modeling

Establishing the relationship of drug concentrations (exposure) to driving ability test endpoints (response) may be useful in interpreting driving studies. The exposure-response relationship may provide insight into dosing regimens not studied directly, predict the effect of various intrinsic/extrinsic factors on driving study endpoints, suggest dose adjustments in subpopulations, and inform labeling. Therefore, sponsors should collect time-matched data on appropriate drug and metabolite exposure and driving ability test endpoints. Sponsors should use regression techniques to analyze the relationship between drug or metabolite concentrations and changes in the endpoints. General considerations for exposure-response analysis can be found in the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.[5]

V. LABELING

Studies to evaluate an important safety endpoint such as driving impairment should be described in the CLINICAL STUDIES section of labeling, including a brief description of the design (e.g., population studied, endpoints, statistical analysis methods) and pertinent results.[6] Safety information from driving studies should be included in other sections of labeling as appropriate, including but not limited to, WARNINGS AND PRECAUTIONS, PATIENT COUNSELING INFORMATION, and FDA-approved patient labeling (e.g., patient information, Medication Guide).

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.