Evaluating Drug Effects on the Ability to Operate a Motor Vehicle

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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TABLE OF CONTENTS

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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 the FDA-regulated drugs for which such evaluation may be needed,[2] and the types of studies that such an evaluation entails. This draft guidance is intended to serve as a focus for continued discussions among the FDA, pharmaceutical sponsors, the academic community, and the public.

This guidance does not address the specific methods or instruments used to collect data on driving ability; rather, the 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. Discussions with the appropriate review division about the methods to be used should take place for specific drug development programs.

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 a great diversity of effects on function, including intended effects and secondary effects (e.g., impaired consciousness from hypoglycemia, impaired vision from a mydriatic). Therefore, the need to consider possible effects on driving is not restricted to psychoactive drugs, and the approach to evaluating risk for nonpsychoactive drugs should be

[1] This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research (CDER) 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.

guided by drug-specific effects, which may differ substantially from the approaches described in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agengy'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 the ability to judge the extent of one's own impairment. Therefore, patient self-perception is usually not adequate for evaluating the presence or degree of driving impairment, or for adequately mitigating risk. Instead, objective information about how a drug affects driving may be needed to enable safe use.

III. THE NEED TO EVALUATE DRIVING IMPAIRMENT

The first considerations in determining whether the effect of a drug on driving should be evaluated are the conditions for use of the drug and the intended patient populations. Drugs intended for chronic (including chronic-intermittent) outpatient use by adults who drive are most likely to need evaluation of effects on driving. In contrast, drugs limited to use in young children or to use in hospital inpatient settings would not need such evaluation. Early discussions with the appropriate review division are recommended to determine whether studies are needed in any given development program to evaluate drug effects on driving.

Drugs with pronounced central nervous system (CNS) impairing effects that 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 might appear to have the potential to *improve* driving performance, for example by decreasing somnolence (an established risk factor in MVAs). However, drugs can have additional effects that increase the likelihood of driving impairment; for example, CNS stimulants might increase risk-taking. Consequently, additional data on other functions important for safe driving should be considered for any psychoactive drug.

Driving studies also may be needed 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. For example, drugs with well-known CNS depressant activity, such as barbiturates and benzodiazepines, have been used over wide ranges of doses and schedules for a number of indications, from anxiety to insomnia to general anesthesia. Potential effects on driving ability might differ among the variety of uses and patient populations.

The driving impairment studies described in this guidance may be impossible to conduct in the intended patient population or need modification for drugs associated with serious safety risks that prevent enrollment of healthy volunteers. 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.

IV. TIERED APPROACH TO EVALUATING DRUG EFFECTS ON DRIVING

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

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

A drug's effect on driving ability cannot be assessed using the risk of actual MVAs because randomized controlled trials using MVAs as an endpoint would be unethical and too large to conduct. Instead, studies that assess the effects of a drug on CNS functions necessary for safe driving should be used to assess the potential for causing MVAs.

The concept of *driving impairment* is complex, and involves the assessment of multiple patient cognitive and sensorimotor functions. It is also critical to relate impairment to the pharmacokinetics and dose of the drug. Driving impairment cannot be fully defined by any single domain, such as alertness; however, evidence of clinically meaningful impairment of even

[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 single domain may be sufficient to conclude that the drug impairs driving, and may provide an adequate basis for regulatory action.

A. Pharmacology/Toxicology

The chemical structure or receptor binding profile of a drug can suggest the potential to affect abilities relevant to driving. For example, drugs with a benzodiazepine structure or that promote binding of gamma-aminobutyric acid to its receptors are likely to have CNS depressant effects, and will need close attention to depressant effects in clinical studies. However, structure and receptor binding alone may not be sufficient to conclude a drug does *not* impair abilities relevant to driving, as cortical functions such as judgment are not well-assessed in nonclinical 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 to evaluating the risk that a drug may cause impairment at a time when patients are driving. Plasma or brain tissue half-life is particularly important for drugs intended to be active primarily, or only, at night, or at other times when patients are 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 that are caused in part by 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 primary and secondary pharmacologic targets of the drug, in vitro/in vivo functional 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. The pharmacological activity and pharmacokinetics of major circulating metabolites in humans, as well as the parent compound, should be taken into consideration.

B. Epidemiology

Epidemiological data about drug adverse effects should be interpreted in the context of confounding by indication and other potential biases, but 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. Epidemiological data can be particularly useful for understanding how various factors related to actual clinical use (e.g., drug-disease interactions, drug-drug interactions, and dosing errors) might impact the effect of a new drug on driving safety. Epidemiological studies may provide information about risk among actual users of the drug who may differ in important ways from the population studied in clinical trials.

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]

[4] LeRoy, A and ML Morse, 2008, Multiple Medications and Vehicle Crashes: Analysis of Databases, U.S. Department of Transportation, National Highway Traffic Safety Administration, DOT HS 810-858.

Although the focus of this guidance is limited to drug effects on driving, it may be important to take epidemiological information into consideration when designing or interpreting driving studies.

Epidemiological data, however, are generally poorly suited to providing convincing evidence that a drug or drug class does *not* increase the risk of MVAs or cause clinically meaningful driving impairment. MVAs are common, and even in patients with clinically meaningful impairment, many other factors contribute to the occurrence of a collision, decreasing the power of epidemiological studies to identify increased risk reliably. Patient population and other disease-specific factors can also have a large effect on MVA risk, but are difficult to characterize and adjust for in epidemiological studies.

Postmarketing adverse event reports are of limited use for identifying drugs that impair driving because of inability to verify critical circumstances of use such as dose and concomitant use of other drugs or alcohol, but may suggest that a drug increases MVA risk under certain circumstances. Such reports are of essentially no use for demonstrating that a drug lacks meaningful adverse effects on driving, because of the high background rate of MVAs, and the recognized relation of MVAs to age, sex, driving experience, and many other factors that are poorly documented in postmarketing reports. In addition, under-reporting may occur if patients and providers are not aware that impairment from a drug may have contributed to an MVA.

C. Phase 1 Drug Development Studies

Beginning with first-in-human studies, 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 adverse CNS events in even a small number of phase 1 subjects can indicate the need for more focused studies of CNS effects.

Early testing for CNS effects should generally emphasize sensitivity over specificity. Various psychomotor and neuropsychological tests, including measures of reaction time, divided attention, selective attention, and memory may be appropriate. Early studies often include higher doses than will be used in later efficacy studies, which provides an opportunity to explore CNS effects over a substantial portion of the exposure-response curve. 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 effects (e.g., by visual analogue scale) can contribute important information about the degree of subjective awareness of objectively demonstrated drug-related impairment.

If there is initial evidence of impairing effects, additional phase 1 studies should examine CNS impairment over the full range of drug exposures that may occur in phase 2 and 3 studies. Studies should include consideration of active metabolites, and exposure in subpopulations that might have higher exposure, such as from genetic polymorphism of metabolizing enzymes.

A positive control in studies of CNS effects is critical for study interpretability. Negative studies in the absence of demonstrated assay sensitivity are generally 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 can be discussed with the FDA.

D. Phase 2 and 3 Studies

For drugs with potential effects on driving (e.g., any drug with sedating properties or drugs suspected of impairing driving ability during early testing), drug blood levels, including major active metabolites, should be measured in phase 2 and 3 studies. Factors that affect blood levels, such as time of dosing, should be documented. Unexpectedly high drug blood levels (i.e., *outliers*) should be confirmed in repeat testing to determine whether they resulted from methodological issues or represented interpatient variability.

For drugs identified in early development as having a high potential to cause impairment, patients should be monitored in phase 2 and 3 studies for signs and symptoms of psychoactive effects that could place the individual at unacceptable risk. While this monitoring should be guided by adverse effects elicited in earlier-phase testing, such as 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 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).

Both open-ended and targeted questions regarding adverse effects should be used. Specific patient-reported outcomes that measure symptoms of concern, such as *sleepiness scales*, can help to quantify severity. Investigators should ask patients (and family members when appropriate) about their perception of driving ability; negative responses provide limited reassurance of safety, but positive reports of difficulty staying awake while driving or collision *near misses* are clearly of concern. Objective tests of psychomotor function, as described in section IV.C., Phase 1 Drug Development Studies, may also be needed to protect patient safety adequately. For example, for trials of insomnia drugs, all enrolled patients through phase 3 studies typically are tested at intervals throughout the study for daytime psychomotor impairment, using both subjective and objective measures.

In phase 2 and 3 studies, the time of day and duration of CNS adverse effects should be documented, because this information can characterize temporal effects on the risk of driving impairment. Patients should be specifically queried about the occurrence of adverse drug effects while driving. Sponsors are also encouraged to collect data on actual MVAs and traffic violations in phase 3 studies, although such events are generally infrequent.

E. Driving Studies

If accumulating data suggest a potential for driving impairment, dedicated *driving studies* with higher face validity than more general tests of CNS function may be needed to refine assessment of the clinical effect of impairment. Such studies can be carried out with either actual motor vehicles or driving simulators.

Driving is a multifaceted activity and any given *driving test* may not be capable of characterizing all of the different types of drug effects that can impair driving. 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.

Positive control and placebo groups should be included 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 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. A positive control might be a drug that the FDA has approved with detailed labeling regarding driving impairment.

Enrolling patients in driving studies who are from the population likely to use the drug, including the elderly, instead of healthy volunteers, is almost always important to inform about disease-drug interactions. However, in some cases it might be possible to conclude that differences between healthy volunteers and patients are sufficiently small that healthy volunteers can be studied.

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

Studies of driving impairment should assess drug effects at the highest exposures expected to be encountered in clinical use. This includes exposures that might be experienced by patients taking allowed concomitant medications, or patients with specific genetic traits or other characteristics that could lead to higher exposures from the same dose. Studying doses higher than intended for marketing can be a useful strategy for gathering such information in an otherwise unselected population of study subjects.

For certain drugs intended to be dosed at night, including drugs for sleep disorders, adverse CNS effects *cannot* be assumed to be absent at the lower levels expected during the following day, especially in the morning, and focused studies of CNS effects during the day after dosing, as guided by blood levels, may be needed to characterize the risk of driving.

F. Randomization

A typical randomization scheme is described below for testing both the acute (1 dose) and more chronic (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 at least grossly matching 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

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

G. Endpoint Analysis

Although analysis of safety endpoints based on mean effect can be informative, exposure (e.g., C_{max}, area under the curve, tissue levels) from many drugs varies among patients by an order of magnitude or more. Thus, clinically meaningful impairment in patients at the high end of drug exposure might not be detected by mean changes. Differences in pharmacodynamic sensitivity among patients, while generally less well understood than differences in drug exposure, can also render an analysis of mean changes insensitive to clinically meaningful impairment in a subset of patients.

Some of the shortcomings of an endpoint based on average effects can be addressed by a responder analysis that assesses the *proportion* of patients on drug versus placebo that exceed a predetermined threshold for clinically meaningful impairment, or other thresholds, larger and smaller, that are of interest in understanding the degree of impairment. The statistical test used for such an analysis has been called a *symmetry analysis* because it tests whether the distribution

of changes (drug minus placebo) above the threshold and below the threshold is symmetric around zero.[5]

H. Exposure-Response Modeling

Establishing the relationship of drug concentrations (exposure) to driving test endpoints (response) may be useful in planning and 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 test endpoints, suggest dose adjustments in subpopulations, and inform labeling. Therefore, time-matched data on appropriate drug and metabolite exposure and driving test endpoints should be collected. The relationship between drug or metabolite concentrations and changes in the endpoints should be analyzed using regression techniques. General considerations for exposure-response analysis can be found in the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications.*[6]

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.[7] 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] Laska, E, M Meisner, J Wanderling, 2012, A Maximally Selected Test of Symmetry About Zero, Stat Med, 31:3178-91.

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

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