CRC COGNITIVE RESEARCH CORPORATION

COMPLIANCE WITH 2017 FDA GUIDANCE FOR EVALUATING DRUG IMPAIRED DRIVING

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OBJECTIVE

The US Food and Drug Administration *(FDA)* issued final guidance entitled "Evaluating Drug Effects on the Ability to Operate a Motor Vehicle" in November 2017 *(See Table 1)*. The purpose of this presentation is to report on how this guidance has been applied to drugs subsequently approved by the FDA *(January 2018 - July 2024)*.

DESIGN

The FDA website *(www.fda.gov)* served as the source of information. A listing was generated of all novel drug **approvals** from January 2018 to July 2024. For each drug, the listing included sponsor, drug name, active ingredient, approval date, approved use, whether a drug is used chronically by adults, and whether a driving study had been conducted. In addition, information was recorded regarding driving-relevant Adverse Events *(AEs)*. Authors, utilizing the FDA final guidance, judged whether each of the drugs warranted a dedicated driving study.

RESULTS

Of the 377 FDA-approved drugs (from January 2018 - July 2024), 4 drugs underwent a dedicated driving study. All 4 of these drugs are CNS drugs for psychiatry or neurology indications. Based upon the conservative application of FDA criteria, there were 40 drugs that clearly met FDA criteria for a dedicated driving study. A number of other drugs were identified as having adverse events (somnolence, fatigue, dizziness, sedation, blurred vision), raising concerns for potential effects on driving. Multiple examples were found where the approved drug label warns against driving, but no driving study was conducted.

Analysis by therapeutic area shows that of the 40 drugs identified as meeting criteria for a dedicated driving study, 18 are CNS drugs, 12 are Oncology drugs, and the remainder (10) are from a range of therapeutic areas (e.g., infectious disease, genetic disorders). Further analysis, specifically of the CNS drugs, suggests that for certain psychiatric conditions (e.g., schizophrenia) drugs are considered exempt from driving study requirements, perhaps based on an assumption that these patients do not drive.

CONCLUSION

Since the finalization of the FDA Guidance for Evaluating Drug Effects (in 2017), 40 of the 377 approved drugs appear to meet the criteria for requiring a dedicated driving study. However, only 4 of these 40 drugs underwent a dedicated driving study. Notably, 14 of the drugs approved without a driving study are CNS drug approvals. Based on this investigation, it appears that dedicated driving studies are not routinely being performed on drugs that are likely to impair driving when used chronically on an outpatient basis by adults.

DISCLOSURES: Drs. Kay & Hochadel are employees and shareholders of Cognitive Research Corporation. Ms. Isaacks is an employee of Cognitive Research Corporation.

TABLE 1
KEY POINTS FROM FDA GUIDANCE

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. The guidance outlines the general principles and goals of such studies.

BACKGROUND: Driving is a complex activity involving a wide range of cognitive, perceptual, and motor activities. 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.

NEED TO EVALUATE DRIVING IMPAIRMENT: Drugs intended for chronic (including chronic-intermittent) outpatient use by adults are most likely to need evaluation of effects on driving ability. 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. 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.

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**.

TABLE 2
APPROVED DRUGS FOR WHICH DRIVING STUDY WAS PERFORMED

DRUG NAME	INDICATION	MARKED CNS AEs	TYPE OF DRIVING STUDY	DRIVING LABEL / WARNINGS
DAYVIGO	Insomnia	Impairment of daytime wakefulness; next-day somnolence; sleep-driving	Over the road	Do not drive, operate heavy machinery, do anything dangerous, or do other activities that require clear thinking if you take DAYVIGO and have had less than a full night of sleep *(at least 7 hours)* or if you have taken more DAYVIGO than prescribed by your healthcare provider. Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAYVIGO.
REYVOW	Migraine / Pain	CNS depression, dizziness, fatigue, paresthesia, and sedation	Simulator	Advise patients not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery for at least 8 hours after taking each dose of REYVOW. Patients may not be able to assess their own driving competence and the degree of impairment caused by REYVOW.
QUVIVIQ	Insomnia	Headache, somnolence, fatigue; Impairs alertness and motor coordination	Simulator	The risk of daytime impairment is increased if QUVIVIQ is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken. If QUVIVIQ is taken in these circumstances, caution patients against driving and other activities requiring complete mental alertness.
ZURZUVAE	Postpartum Depression	CNS depressant effects; Somnolence, confusion, dizziness, fatigue	Simulator	ZURZUVAE causes driving impairment due to central nervous system *(CNS)* depressant effects. Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration. Patients may not be able to assess their own driving competence or the degree of impairment caused by ZURZUVAE.

TABLE 3
EXAMPLES OF APPROVED DRUGS WITH CNS AES BUT NO DRIVING STUDY

DRUG NAME	INDICATION	MARKED CNS AEs	DRIVING LABEL / WARNINGS
LYBALVI	Schizophrenia / Bipolar	Dizziness, somnolence, sedation, headache, asthenia, tremor	Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LYBALVI therapy does not affect them adversely.
KYNMOBI	Parkinson's Disease	Falling asleep during activities of daily living and daytime somnolence; May cause hallucinations, psychotic-like behavior; paresthesia, dizziness, somnolence	Instruct patients not to drive a car or engage in other potentially dangerous activities until they have gained sufficient experience with KYNMOBI to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) occur, they should not drive or participate in potentially dangerous activities until they have discussed this with their healthcare provider.
AYVAKIT	Oncology	Memory impairment, cognitive disorder, confusional state, disturbance in attention, amnesia, mental impairment, mental status changes, abnormal thinking, drowsiness, somnolence, insomnia, dizziness, headache	Advise patients not to drive or operate hazardous machinery if they are experiencing cognitive adverse reactions.
QDOLO	Pain	Dizziness/vertigo, somnolence; May impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Anxiety, Confusion	Inform patients that QDOLO may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.