FDA Recommends Testing Drugs for Impacts on Driving Ability

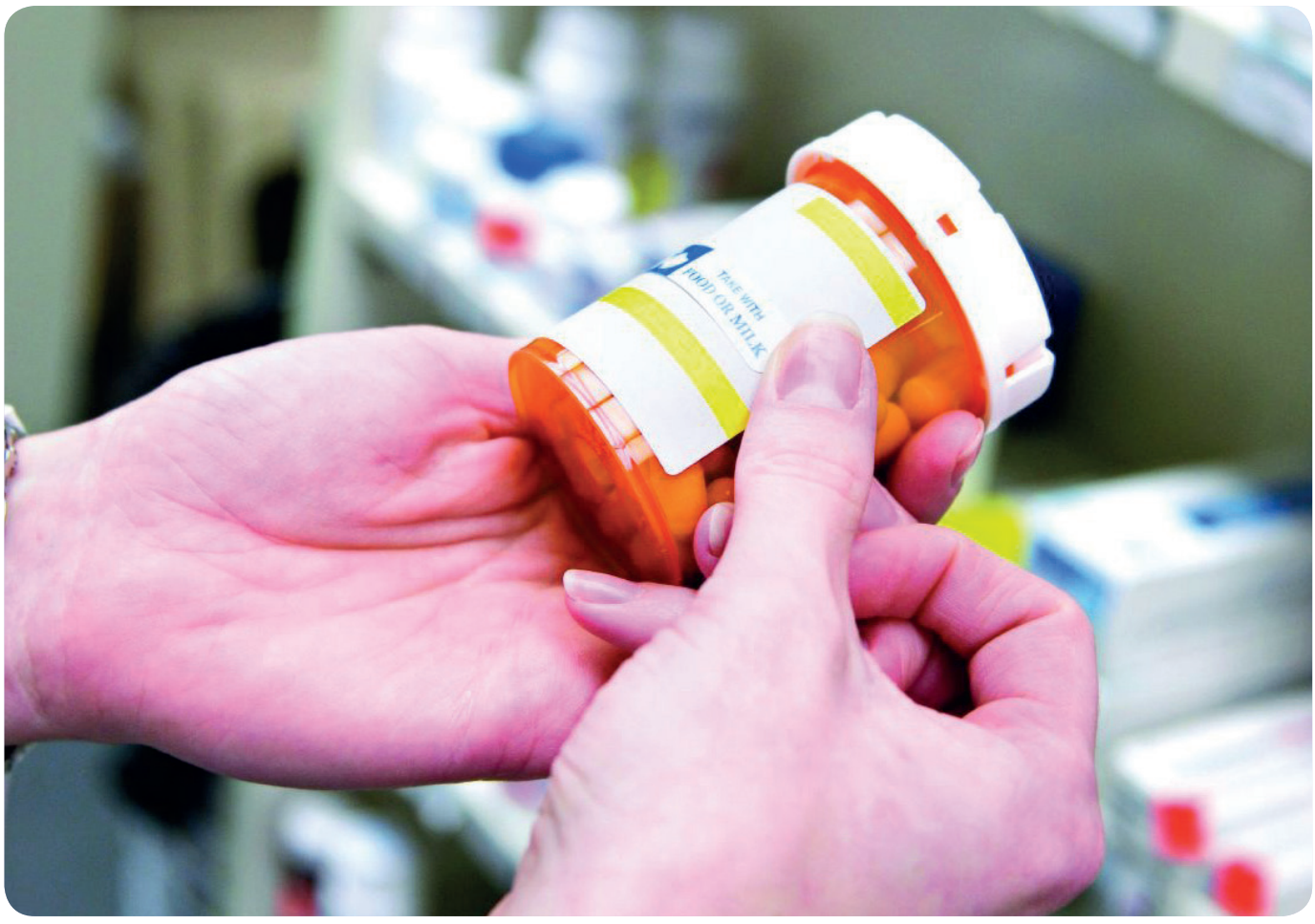
New US Food and Drug Administration (FDA) draft guidance addresses when and how to evaluate drugs for the potential to impair driving ability, an issue that arises during agency reviews of approved and investigational products. Next-day drug effects are of particular concern during reviews of insomnia treatments, which are, of course, intended to sedate. In mid-May 2014, for example, the FDA announced it would require Sunovion Pharmaceuticals Inc to reduce the starting dose for prescription sleep aid Lunesta (eszopiclone) after post-market study found that the recommended doses impaired some patients' psychomotor coordination and memory for as long as 11.5 hours.

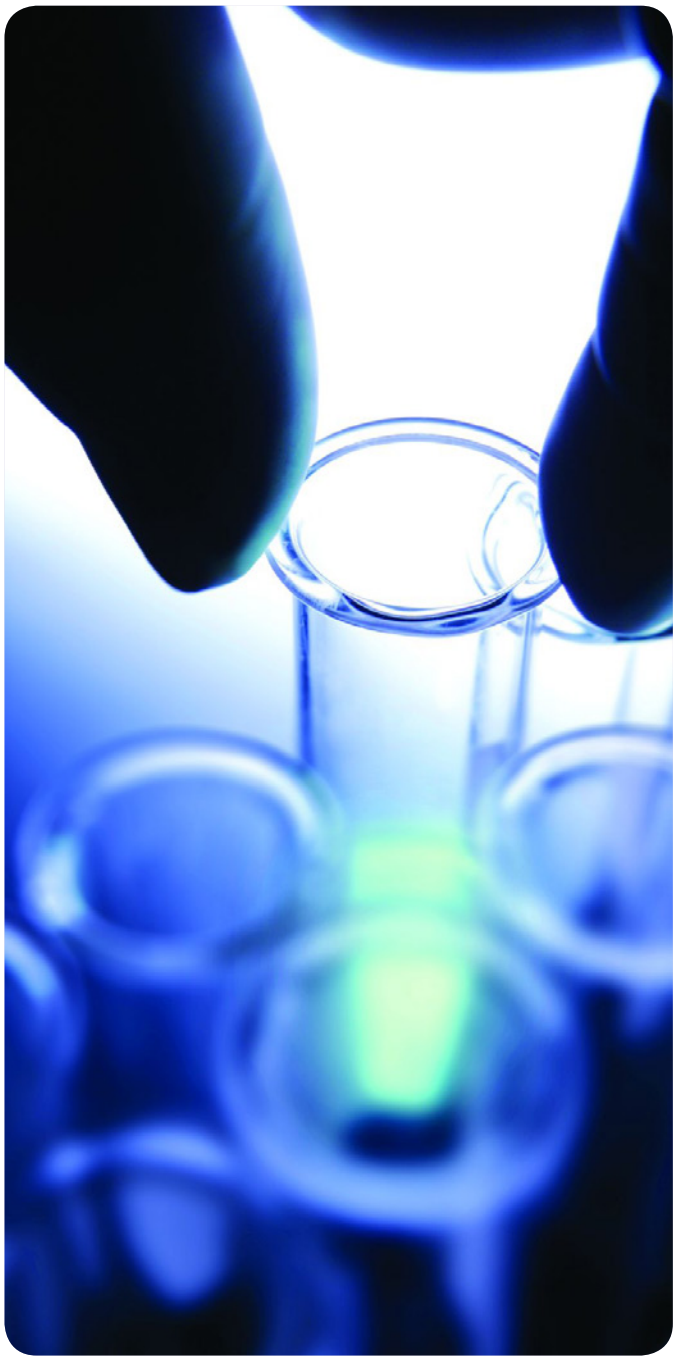
The new draft guidance, issued in January 2015, focuses on psychoactive drugs, noting particular concern for night-time products that markedly impact the central nervous system. *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle* is the first formal guidance issued by the FDA on this topic. The document outlines the principles and goals of studies rather than specific methods or instruments. It discusses Phase I studies, Phase II/III studies, and driving studies, and addresses issues such as randomisation and endpoint analysis.

The FDA recommends a "tiered approach" to evaluating impaired driving, including pharmacological/toxicological, epidemiological, and standardised behavioural assessments. The need for and focus of later-stage tests depend on findings earlier on. Several "broad functional domains" contribute to a person's driving ability and should be evaluated, according to the guidance, including:

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

While none of these domains alone thoroughly defines driving ability or impairment, if a drug causes "clinically meaningful impairment" to a single domain, that evidence may be enough to conclude the drug impairs driving, according to the guidance. The FDA specifically notes that for some products, including drugs for sleep disorders, adverse effects on the central nervous system "cannot be assumed to be absent" the following day. Focused studies, guided by blood levels, may be necessary to characterise driving risk.





The FDA reduced the Lunesta start dose to 1 mg for all adults after finding that 2 and 3 mg doses impaired alertness for as long as 11.5 hours in some patients, affecting their driving skills, coordination, and memory. The revised Lunesta product label also cautions that the drug caused some patients to perform activities they could not recall the next day, such as "sleep-driving," making phone calls, eating, sleep-walking, and engaging in sex. While higher Lunesta doses may be appropriate for some, patients should always use the lowest effective dose, the label states. Anyone taking 3 mg "should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use."

The Lunesta dose change followed reductions in January 2013 to the recommended doses of products containing another sedative, zolpidem, including Ambien, by sanofi-aventis US LLC. The FDA required those reductions after data from post-market driving simulation and lab studies showed that the morning-after zolpidem blood level for some patients was high enough to impair driving, increasing the risk for accidents. The zolpidem dose change came 20 years after the product's initial FDA approval, in December 1992.

In May 2014, the FDA convened experts to consider suvorexant, an investigational sleep aid proposed by Merck Sharp & Dohme Corp. While members of the Peripheral and Central Nervous System Drugs Advisory Committee strongly supported the drug's efficacy, their discussions returned frequently to concerns about next-day safety, including "excessive daytime sleepiness." An FDA review of Merck's clinical trial data had found that suvorexant "clearly" caused dose-related, next-day effects, including sedation, as noted in the agency's briefing materials for the meeting.

Of particular significance to the FDA were formal driving study results showing that suvorexant can cause significant driving impairment (specifically, excessive deviation in lane position) the morning after dosing. Merck had conducted two randomised, double-blind, placebo- and active-controlled, four-period crossover studies to assess the effects of suvorexant on next-day driving performance.

Merck received FDA approval for suvorexant, now marketed as Belsomra, in August 2014. Although Merck requested a recommended dose of 20 mg for non-elderly adults and 15 mg for elderly, the FDA approved a recommended dose of just 10 mg for all adults. The *maximum* approved dose is 20 mg once daily, far lower than Merck's proposed recommended daily dose of 40 mg for non-elderly adults and 30 mg for elderly. In addition, the Belsomra label includes warnings for daytime somnolence, noting a dose-related risk for impaired driving. It also advises that patients taking 20 mg should be cautioned "against next-day driving and other activities requiring complete mental alertness," and states that all Belsomra users should be warned about the risk of potential driving impairment.

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