

# FDA Guidance Backs Earlier Clinical Drug Testing

BY MARY ELLEN SCHNEIDER  
Senior Writer

Researchers now have a pathway for conducting early clinical testing of drugs in a small number of human subjects under new guidance from the Food and Drug Administration.

Officials at the FDA finalized guidance on exploratory investigational new drug (IND) studies which allows researchers to move forward with small human studies

before beginning traditional phase I safety testing in humans. The guidance, published in January, makes recommendations on safety testing, manufacturing, and clinical approaches in these early studies.

The FDA also published draft guidance and a direct final rule that outlines new standards for the manufacture of drugs solely for use in phase I studies. The rule is aimed at making it easier for scientists to produce small quantities of drugs for small-scale, early-phase human testing.

"This is about saving lives and about building medicine's future," said Dr. Andrew von Eschenbach, acting FDA Commissioner of Food and Drugs.

Currently, less than 10% of IND applications for new molecular entities progress beyond the investigational stage, according to the FDA. These changes will remove some of the hurdles from very early drug development, Dr. von Eschenbach said during a media teleconference sponsored by the FDA.

But critics of the approach say it relaxes needed human subjects protections at a time when the safety of clinical trials is already being questioned.

In guidance on the exploratory IND, FDA officials outline their thinking that drug sponsors have not taken full advantage of the flexibility in the existing regulations and often provide more supporting information than is required for an exploratory IND.

Exploratory IND studies involve administering either a subpharmacologic dose of a product or doses that are expected to produce a pharmacologic but not a toxic effect, so the risk to human subjects is considered lower than in a traditional phase I study, the FDA said in its guidance documents.

Since exploratory IND studies pose fewer risks, the FDA said, they can be initiated

## Excessive **ES** Sleepiness

## Hypersomnolence: A Multidimensional Impact on Life

By definition, hypersomnolence (excessive sleepiness, or ES) consists of unintended periods of drowsiness or sleepiness that occur during desired waking periods.<sup>1</sup> ES is associated with narcolepsy, obstructive sleep apnea (OSA), and shift work sleep disorder (SWSD), and it can also be caused by multiple sclerosis, Parkinson's disease, mood disorders, and many other neurological and psychological disorders.<sup>1</sup> Regardless of the cause, ES can impact life in ways that merit further consideration.

### Job performance reexamined

True ES symptoms should be differentiated from fatigue, tiredness, and lack of motivation, all of which may be perceived by employers as laziness.<sup>2</sup> Patients with untreated OSA, narcolepsy, or other disorders with ES are more likely to be involved in work-related accidents than the general public, and to incur higher healthcare-related costs.<sup>3</sup>

### Driving while impaired

The effects of ES do not end with the workday. ES can adversely affect concentration, so it is not surprising that the risk of auto accidents is higher in people who experience ES, such as shift workers and people with undiagnosed sleep disorders.<sup>4</sup> The drive home after a full workday can be the most hazardous part of the day for a patient with ES.

### Family and social consequences

ES can impair a patient's spousal or family relationships, too. The consequences of chronic ES may include mild to severe fatigue, crankiness, and home accidents.<sup>5</sup> Poor motor, mental, and cognitive function at home can significantly impact a patient's quality of life.<sup>6</sup>

### ES and cognitive performance

Patients may experience symptoms of "executive dysfunction" accompanying excessive sleepiness, including impaired verbal fluency, serial learning deficits, problems focusing attention, and concentration difficulties.<sup>3</sup> Similarly, degree of sleepiness has been correlated with results of psychomotor vigilance task (PVT) studies.<sup>7</sup> Other PVT research confirms that sleep loss and alcohol consumption have a comparable negative effect on psychomotor performance.<sup>8</sup>

Lapses in cognitive efficiency as a result of ES can also be evaluated using the Cognitive Drug Research (CDR) System, which was developed to assess both enhancement and impairment of human cognitive performance in a clinical trial setting.<sup>9,10</sup> In one such use, the CDR System indicated that attention and memory suffered as a result of working long hours in a surgical unit without sleep.<sup>11</sup>

### Wakefulness when wakefulness matters

Importantly, ES is often symptomatic of an underlying condition that merits attention, rather than the result of deficiencies in the quality or quantity of an individual's sleep. Therefore, identification and treatment of the underlying condition are critical priorities. Once the underlying condition has been managed, the clinician may choose to continue to evaluate the effects of ES with the Epworth Sleepiness Scale (ESS), which measures the likelihood of dozing during 8 commonly encountered daytime situations.<sup>12</sup> Once the impact of excessive sleepiness is understood, the clinician can begin to focus on managing ES by extending wakefulness throughout the day.

**For more information about managing ES in your clinical practice, please visit [www.ExcessiveSleepiness.com](http://www.ExcessiveSleepiness.com).**

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The usual protection for human subjects has been 'watered down.'

DR. WOLFE

ed in humans with less, or different, pre-clinical support than what is required for traditional IND studies.

Previously, one of the major obstacles in the development of new drugs was that the requirements for beginning early experimental studies were the same as those for large pharmaceutical companies who are making drugs for thousands of patients, Dr. Steven Rosenberg, chief of surgery at the National Cancer Institute, said during the teleconference.

"We've been at the mercy of large biotech and pharmaceutical companies who have the resources to fulfill the very stringent regulations that exist for taking these new products to very large numbers of patients," he said.

The changes made by the FDA will make it possible for scientists to take new ideas to small numbers of patients with desperate diseases and test those agents in ways that weren't possible before, he said.

But Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, said he remains concerned that the usual protection for human subjects has been "watered down." Under the new process outlined by the FDA, a safety problem that might have been detected through more extensive animal studies now may be missed, he said.

Dr. Wolfe said the types of studies described in the exploratory IND are already being done but with the previous protections in place for human subjects.

Sen. Charles Grassley (R-Iowa), chairman of the Senate Committee on Finance, which has been conducting oversight of the FDA's consumer protections, also expressed safety concerns.

"Of course people want to get safer, better drugs faster, but there have to be sufficient checks and balances in the drug approval process," Sen. Grassley said in a statement.

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