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# **Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment Guidance for Industry**

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

**October 2020  
Clinical/Medical**

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# **Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment Guidance for Industry<sup>1</sup>**

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**

This guidance is intended to help sponsors develop drugs for treatment of opioid use disorder (OUD). This guidance addresses clinical endpoints acceptable for demonstrating effectiveness of such drugs. This guidance does not address the development of drugs intended only to provide symptomatic relief of opioid withdrawal.

For assistance on specific drug development programs to treat OUD, sponsors should contact the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (the division) in the Center for Drug Evaluation and Research.

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**

Treatments for OUD can be initiated in patients who are actively ill and not currently receiving other drug treatments for OUD or in patients who have already discontinued problematic opioid use.<sup>2</sup> Drugs that have opioid agonist activity can be initiated in patients with current problematic use of opioids. However, because of the risk of causing severe withdrawal symptoms, drugs

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<sup>1</sup> This guidance has been prepared by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Center for Drug Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> As used in this guidance, the term *problematic use* refers to drug use in an inappropriate, unsanctioned manner in the context of opioid use disorder. Although the concept is well-understood by patients and treatment providers, some more commonly used terms (typically, *illicit use*) are considered stigmatizing and others (e.g., *abuse*) are ambiguous.

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with opioid antagonist activity cannot be initiated until patients discontinue opioid use. Drugs that are neither agonists nor antagonists can be used in either population.

Patients with OUD may discontinue problematic opioid use through inpatient programs, medically supervised withdrawal, self-initiated discontinuation, or as a result of incarceration. Each of these pathways may or may not include drugs to manage the symptoms of opioid withdrawal. Drugs intended to provide symptomatic relief of opioid withdrawal may support patients completing opioid detoxification but are usually not sufficient to reduce the risk of returning to problematic opioid use. Therefore, these drugs are not covered by this guidance.

Efficacy trials of drugs for treating OUD have typically employed a randomized, blinded, controlled trial design. For drugs intended for use as initial therapy, patients should be new entrants to treatment<sup>3</sup>. Different trial design choices can be employed, including superiority or noninferiority studies (with a prespecified noninferiority margin) using appropriate comparators. Trial designs should generally incorporate standard-of-care nonpharmacologic treatments. Patients experiencing clinical deterioration during the trial should be transferred out of the protocol to receive another OUD treatment appropriate to their clinical condition. The recommended primary efficacy endpoint is the proportion of responders (discussed in section III. D). The effects of the study drug on other (nonopioid) problematic drug use should also be evaluated as a secondary endpoint. The responder definition should be prespecified, taking into account the schedule of assessments, and may incorporate a grace period. Efficacy analyses should include comparison of responder rates, cumulative responder curves,<sup>4</sup> and graphic displays of individual patient responses.

For drugs intended to reduce the risk of relapse, patients already stable<sup>5</sup> on other treatments for OUD should be studied, and the comparator should be an approved therapy. Patients should be seen at frequent intervals and assessed for adverse events and clinical status (including drug-taking behavior measured by urine toxicology screen and self-report of opioid or other problematic drug use, and measures of clinical benefit or function). These trials can employ different designs, including superiority or noninferiority (with a prespecified noninferiority margin).

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<sup>3</sup> For purposes of this guidance, new entrants to treatment are individuals with OUD who regularly use opioids in an unsanctioned manner and whose drug use is having substantial impact on their function. Such patients may or may not have had previous episodes of treatment but are currently not engaged in treatment for OUD.

<sup>4</sup> A cumulative responder curve or cumulative distribution function refers to an approach in which various possible definitions of responder are considered and compared graphically. The graph shows, for example, the percentage of patients who provided a given percentage of negative samples or better. The curves, therefore, fall from 100% at the left to 0% at the right.

<sup>5</sup> For purposes of this guidance, stable patients are those who have been engaged in treatment for OUD for a sustained period of time and have demonstrated a good response. They have ceased problematic drug use or use only very sporadically while receiving treatment. Such patients may or may not meet criteria for full remission under DSM-5. Patients who have been recently started on medication and are titrated to a particular dose are sometimes referred to as *stabilized* because their dose is no longer being titrated, but this is to be distinguished from patients who are clinically stable.

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Since patients with OUD who are new entrants to treatment are considered a more difficult population to treat than patients who are clinically stable, substantial evidence to support effectiveness for the treatment of OUD in new entrants to treatment would typically also support approval for the treatment of OUD in patients who are clinically stable on other approved therapies. However, with respect to OUD, substantial evidence to support effectiveness in stable patients would generally not support approval in new entrants to treatment.

In general, clinical trials evaluating effectiveness of drugs for treating OUD have used reduction in drug-taking behavior (drug use patterns) as an endpoint. There is great interest in expanding the primary and secondary endpoints used in clinical trials of drugs for treating OUD, including other outcome measures important to patients and their families, clinicians, and the public. The following discussion enumerates various outcome measures that could potentially be used as primary and/or secondary endpoints in clinical trials and included in FDA-approved labeling.

### **III. CLINICAL ENDPOINTS**

#### **A. Adverse Outcomes of OUD**

Reductions in adverse outcomes related to OUD are desirable endpoints for study. FDA encourages sponsors to evaluate the effect of drugs in development for OUD on various adverse outcomes.

Examples of these adverse outcomes include:

- Mortality (overall mortality or overdose mortality)
- Need for emergency medical interventions
- Hepatitis C virus infection or reinfection

Sponsors can propose other adverse outcomes and can study several of these endpoints in the same trial, selecting one as the primary endpoint, selecting one or more as secondary endpoints, or combining outcomes in a composite endpoint. Data on background rates of the adverse outcomes in specific target populations would be useful in determining needed sample size and trial duration.

#### **B. Change in Disease Status Using Diagnostic Criteria for OUD**

Diagnostic criteria for OUD encompass drug use and its effect on patient well-being. We recommend that, if all trial patients meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for moderate-severe OUD at baseline,<sup>6</sup> sponsors could use the proportion of patients meeting DSM-5 criteria for remission of OUD at the end of the trial as a primary or secondary efficacy endpoint.

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<sup>6</sup> American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Arlington, Virginia: American Psychiatric Publishing.

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### **C. Change in Drug Use Pattern<sup>7</sup>**

FDA generally accepts change in drug use patterns as a surrogate for the benefits of abstaining from drug taking or for the presumed benefits of reducing drug taking. Change in drug use pattern is the most commonly used endpoint in registration trials for drugs in development to treat OUD. Sponsors have used it successfully to provide support of efficacy for all approved products for treating OUD. Sponsors have used a variety of approaches to evaluate drug use patterns. FDA recommends that sponsors compare percentage of responders rather than group means. One method is to define a responder as a patient who reduces the use of opioids to or below a threshold known to be associated with clinical benefit. A successful trial would show either a higher percentage of responders in the treatment arm (for superiority trials) or noninferiority in the percentage of responders (for active-controlled noninferiority trials).

A commonly used definition for a responder is abstinence, defined as no detected or self-reported use during the specific assessment window. It is not possible to have absolute confidence that a responder achieved complete abstinence. Very frequent measurements provide more assurance of a substantial reduction in drug use, whereas infrequent drug use measurements result in greater uncertainty about the true magnitude of reduction in drug use. For this reason, absence of positive urine drug tests, absence of self-reported drug use, and attendance at frequent scheduled observations for these measures are components of a complete abstinence response definition.

Sponsors can employ drug use patterns other than abstinence to define response to OUD treatment. In proposing other drug use patterns to define clinical response, sponsors should specify how the change in drug use pattern will be measured. Certain changes in drug use patterns, such as *fewer occasions of use per day* or *reduced amount of use per occasion*, may prove impractical to measure. In addition, to support a drug use pattern to define clinical response, sponsors should evaluate and submit evidence from clinical trials, longitudinal prospective observational studies, or other sources of information to show that such reduction in drug use predicts clinical benefit (i.e., better health outcomes or psychosocial function). Sponsors should discuss with the division approaches to measure change in drug use patterns and how evidence of clinical benefit could be generated.

### **D. Patient-Reported Outcomes**

Using input from patients and family members to determine the most concerning symptoms/experiences associated with OUD, sponsors could develop a patient-reported outcome (PRO) instrument to evaluate a direct effect on how patients feel or function (e.g., improvement in sleep or mood).

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<sup>7</sup> *Drug use pattern* refers to the frequency, timing, quantity, and intensity (uses per day or amount per use) of problematic drug use by an individual patient. From a practical standpoint, several of these parameters are infeasible to measure, and the most commonly used parameter is days of use. *Abstinence* refers to zero days of use within an assessment window. The more general phrase *reduction in drug use* is subject to many interpretations, including reduction of group means on quantity or frequency of problematic drug use with no single individual having an improvement in their OUD. The phrase *change in drug use pattern* is used to emphasize that individual patient responses are of interest.

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Sponsors could also use this approach to develop a measure for the intensity of the urge to use opioids. Outcomes on this measure could be used as a secondary endpoint in trials that use behavioral change, such as change in drug use patterns, as a primary endpoint. If sponsors plan to use such a PRO instrument as a secondary endpoint, sponsors should first determine the magnitude of the change in the PRO measure that represents a clinical benefit and how long such change should be maintained in a clinical trial to predict a sustained clinical benefit. Sponsors interested in using a reduction in craving endpoint should contact the division about developing a fit-for-purpose instrument to measure craving or the urge to use opioids to complement other endpoints and to determine how the endpoint correlates with sustained clinical benefit.

In developing any of the PRO instruments mentioned above, sponsors should follow the principles outlined in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).<sup>8</sup>

#### **IV. OTHER OUTCOME MEASURES**

FDA is interested in other outcome measures that sponsors might use to demonstrate clinical benefit of drugs for treating OUD, such as reduction in hospitalizations or improvements in the ability to resume work, school, or other productive activity. FDA recognizes that evaluating these outcomes could require larger trials than those usually conducted for marketing approval. However, collecting data on clinically meaningful outcomes would be highly valuable, and FDA encourages sponsors to consider collecting such data even if not intended to support a regulatory decision. Furthermore, using these outcomes as clinical trial endpoints could provide the basis for inclusion in the FDA-approved labeling. It is of note that *retention in treatment* is not recommended as a stand-alone endpoint. Many features of trial design can produce incentives to remain in treatment without accruing clinical benefit. If a sponsor plans to include novel endpoints in a drug development program for treating OUD, FDA strongly encourages the sponsor to discuss such plans with the division early in the drug development process.

#### **V. BENEFIT-RISK CONSIDERATIONS**

When selecting an endpoint to demonstrate efficacy for a specific product, sponsors should bear in mind that, ultimately, the demonstrated benefit of a product will be weighed against the risk under FDA's drug approval standard (section 505(c) and (d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c) and (d))). If a product is associated with a risk of serious adverse events, more compelling demonstrations of clinical benefit may be needed to outweigh this risk. If the product itself has abuse<sup>9</sup> potential, FDA will consider the positive and negative

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<sup>8</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>9</sup> As used in this guidance, the term *abuse* refers to any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desired psychological or physiological effect.

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public health effects of the drug, including risk of diversion, the drug's potential effect on risks to both patients and nonpatients, such as members of the patient's household (e.g., children, teenagers, visitors, and others). The risks considered include those related to misuse,<sup>10</sup> abuse, OUD, overdose, and accidental exposures, particularly in children.

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<sup>10</sup> As used in this guidance, the term *misuse* refers to any intentional therapeutic use of a drug product in an inappropriate way. Misuse specifically excludes those events that meet the definition of *abuse*.