Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment

Guidance for Industry

DRAFT GUIDANCE

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

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is intended to assist sponsors in developing drugs for medication-assisted treatment of opioid use disorder (OUD). This guidance addresses the clinical endpoints acceptable to demonstrate effectiveness of such drugs.

For advice on specific drug development programs to treat OUD, sponsors should contact the Division of Anesthesia, Analgesia, and Addiction Products (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 treatments for OUD can be initiated in patients who have discontinued illicit opioid use already. Medications that have opioid agonist activity can be initiated in patients who are currently using illicit opioids. However, medications with opioid antagonist activity cannot be initiated until patients discontinue opioid use because of the risk of causing severe withdrawal symptoms. Medications that are neither agonists nor antagonists could conceivably be used in either situation.

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

Patients can discontinue illicit use through a variety of pathways, including inpatient programs, incarceration, self-initiated discontinuation, or medically supervised withdrawal. Each of these may or may not include medications to manage the symptoms of opioid withdrawal. Medications intended to provide symptomatic relief of opioid withdrawal are not considered treatments for OUD, but these medications may be useful as an initial step in bringing patients into treatment with drugs intended to reduce the risk of returning to illicit opioid use.

Efficacy trials of medications for the treatment of OUD have typically employed a randomized, blinded, controlled trial design. For medications intended for use as initial therapy, patients are generally new entrants to treatment (i.e., actively ill and not currently receiving other drug treatments for OUD), and these trials employ active controls with a superiority or noninferiority design. Designs generally incorporate standard-of-care nonpharmacologic treatments as well as active medications available on a *rescue* basis, with patients requiring rescue transferred out of the protocol to standard care. For medications intended to reduce the risk of relapse, patients already stable on other treatments are studied, and in general, the comparator should be an approved therapy. Patients are seen at frequent intervals and assessed for adverse events and clinical response, (including drug-taking behavior measured by urine toxicology screen and self-report of opioid and other drug use, and measures of clinical benefit or function). Active-controlled trials employ either superiority designs or noninferiority designs with a prespecified noninferiority margin. The recommended primary efficacy endpoint is a decrease (for superiority trials) or noninferiority (for active-controlled trials) in use of opioids and other drugs of abuse based on a comparison of responders. The responder definition is prespecified and takes into account the schedule of assessments and may incorporate a grace period. Efficacy analyses include comparison of responder rates, continuous responder curves, and graphic displays of individual patient responses.

In general, clinical trials evaluating effectiveness of medications for the treatment of OUD for regulatory purposes have used reduction in drug-taking behavior (drug use patterns) as an endpoint. FDA accepts drug use patterns as surrogates for the benefits of abstinence from drug taking or presumed benefits of reduction of drug taking.

There is great interest in expanding the primary and secondary endpoints used in clinical trials of medications for the treatment of OUD, including outcome measures important to patients and their families, clinicians, and the public. The following discussion enumerates various outcome measures that could potentially be 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. However, to show effects on physical or psychosocial consequences of opioid abuse, trials may need to study a large number of patients for a long period of time. This may make such studies impractical to support initial marketing approval. Nevertheless, FDA encourages sponsors to evaluate the effect of medications 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 seroconversion

The sponsor can study several of these endpoints in the same trial, with one selected as the primary endpoint and one or more selected as secondary endpoints. 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 both drug use and its effect on patient well-being. If all trial patients meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for moderate-severe OUD at baseline,[2] the sponsor 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.

C. Patient-Reported Outcomes

The sponsor could develop a patient-reported outcome (PRO) instrument based on the principles outlined in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*[3] Using input from patients and family members to determine the most concerning symptoms/experiences associated with OUD, the sponsor could develop an instrument to evaluate a direct effect on how patients feel or function (e.g., improvement in sleep or mood).

The sponsor 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 the sponsor plans to use such a PRO instrument as an efficacy endpoint, the sponsor 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 for *craving* or *the urge to use* opioids to complement other endpoints and to determine how the endpoint correlates with sustained clinical response.

[2] American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Arlington, Virginia: American Psychiatric Publishing.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

D. Change in Drug Use Pattern

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 the treatment of OUD. Sponsors have used a variety of approaches to evaluate drug use patterns. FDA recommends that sponsors compare percent 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 percent of responders in the treatment arm (for superiority trials) or noninferiority in the percent of responders (for active-controlled trials).

A commonly used threshold for a responder is abstinence. *Abstinence* is 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 magnitude of reduction in drug use. For this reason, both absence of positive urine drug tests and attendance at scheduled observations are components of a complete abstinence response definition.

Sponsors and other stakeholders often mistakenly believe that using a change in drug use patterns as the endpoint always requires complete abstinence. However, the sponsor could employ drug use patterns other than *abstinence* as thresholds to define response to OUD treatment. In proposing other drug use patterns as response-defining thresholds, the sponsor 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 as a response-defining threshold, the sponsor should evaluate and submit evidence from clinical trials, longitudinal 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.

IV. OTHER OUTCOME MEASURES

FDA is interested in other outcome measures that sponsors might use to demonstrate clinical benefit of medications for the treatment of OUD. There is great societal interest in assessing additional, clinically meaningful endpoints such as reduction in hospitalizations, emergency department visits, overdose, and death as well as 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, the collection of 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, the use of these outcomes as clinical trial endpoints could provide the basis for inclusion in the FDA-approved labeling. *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 the treatment of OUD, FDA strongly encourages the sponsor to discuss such plans with the division early in the drug development process.