
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DRAFT GUIDANCE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)**

**August 2018
Clinical/Medical**

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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	CLINICAL ENDPOINTS	2
	A. Adverse Outcomes of OUD.....	2
	B. Change in Disease Status Using Diagnostic Criteria for OUD.....	3
	C. Patient-Reported Outcomes	3
	D. Change in Drug Use Pattern.....	4
IV.	OTHER OUTCOME MEASURES.....	4

1 **Opioid Use Disorder: Endpoints for Demonstrating**
2 **Effectiveness of Drugs for Medication-Assisted Treatment**
3 **Guidance for Industry¹**
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7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
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15 **I. INTRODUCTION**
16

17 This guidance is intended to assist sponsors in developing drugs for medication-assisted
18 treatment of opioid use disorder (OUD). This guidance addresses the clinical endpoints
19 acceptable to demonstrate effectiveness of such drugs.
20

21 For advice on specific drug development programs to treat OUD, sponsors should contact the
22 Division of Anesthesia, Analgesia, and Addiction Products (the division) in the Center for Drug
23 Evaluation and Research.
24

25 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
26 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
27 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
28 the word *should* in Agency guidances means that something is suggested or recommended, but
29 not required.
30

31
32 **II. BACKGROUND**
33

34 Treatments for OUD can be initiated in patients who are actively ill and not currently receiving
35 other drug treatments for OUD, or treatments for OUD can be initiated in patients who have
36 discontinued illicit opioid use already. Medications that have opioid agonist activity can be
37 initiated in patients who are currently using illicit opioids. However, medications with opioid
38 antagonist activity cannot be initiated until patients discontinue opioid use because of the risk of
39 causing severe withdrawal symptoms. Medications that are neither agonists nor antagonists
40 could conceivably be used in either situation.
41

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.

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

48
49 Efficacy trials of medications for the treatment of OUD have typically employed a randomized,
50 blinded, controlled trial design. For medications intended for use as initial therapy, patients are
51 generally new entrants to treatment (i.e., actively ill and not currently receiving other drug
52 treatments for OUD), and these trials employ active controls with a superiority or noninferiority
53 design. Designs generally incorporate standard-of-care nonpharmacologic treatments as well as
54 active medications available on a *rescue* basis, with patients requiring rescue transferred out of
55 the protocol to standard care. For medications intended to reduce the risk of relapse, patients
56 already stable on other treatments are studied, and in general, the comparator should be an
57 approved therapy. Patients are seen at frequent intervals and assessed for adverse events and
58 clinical response, (including drug-taking behavior measured by urine toxicology screen and self-
59 report of opioid and other drug use, and measures of clinical benefit or function). Active-
60 controlled trials employ either superiority designs or noninferiority designs with a prespecified
61 noninferiority margin. The recommended primary efficacy endpoint is a decrease (for
62 superiority trials) or noninferiority (for active-controlled trials) in use of opioids and other drugs
63 of abuse based on a comparison of responders. The responder definition is prespecified and
64 takes into account the schedule of assessments and may incorporate a grace period. Efficacy
65 analyses include comparison of responder rates, continuous responder curves, and graphic
66 displays of individual patient responses.

67
68 In general, clinical trials evaluating effectiveness of medications for the treatment of OUD for
69 regulatory purposes have used reduction in drug-taking behavior (drug use patterns) as an
70 endpoint. FDA accepts drug use patterns as surrogates for the benefits of abstinence from drug
71 taking or presumed benefits of reduction of drug taking.

72
73 There is great interest in expanding the primary and secondary endpoints used in clinical trials of
74 medications for the treatment of OUD, including outcome measures important to patients and
75 their families, clinicians, and the public. The following discussion enumerates various outcome
76 measures that could potentially be included in FDA-approved labeling.

79 III. CLINICAL ENDPOINTS

81 A. Adverse Outcomes of OUD

82
83 Reductions in adverse outcomes related to OUD are desirable endpoints for study. However, to
84 show effects on physical or psychosocial consequences of opioid abuse, trials may need to study
85 a large number of patients for a long period of time. This may make such studies impractical to
86 support initial marketing approval. Nevertheless, FDA encourages sponsors to evaluate the
87 effect of medications in development for OUD on various adverse outcomes.

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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>.

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129 **D. Change in Drug Use Pattern**

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131 Change in drug use pattern is the most commonly used endpoint in registration trials for drugs in
132 development to treat OUD. Sponsors have used it successfully to provide support of efficacy for
133 all approved products for the treatment of OUD. Sponsors have used a variety of approaches to
134 evaluate drug use patterns. FDA recommends that sponsors compare percent of responders,
135 rather than group means. One method is to define a responder as a patient who reduces the use
136 of opioids to or below a threshold known to be associated with clinical benefit. A successful trial
137 would show either a higher percent of responders in the treatment arm (for superiority trials) or
138 noninferiority in the percent of responders (for active-controlled trials).

139
140 A commonly used threshold for a responder is abstinence. *Abstinence* is defined as no detected
141 or self-reported use during the specific assessment window. It is not possible to have absolute
142 confidence that a responder achieved complete abstinence. Very frequent measurements provide
143 more assurance of a substantial reduction in drug use whereas infrequent drug use measurements
144 result in greater uncertainty about the magnitude of reduction in drug use. For this reason, both
145 absence of positive urine drug tests and attendance at scheduled observations are components of
146 a complete abstinence response definition.

147
148 Sponsors and other stakeholders often mistakenly believe that using a change in drug use
149 patterns as the endpoint always requires complete abstinence. However, the sponsor could
150 employ drug use patterns other than *abstinence* as thresholds to define response to OUD
151 treatment. In proposing other drug use patterns as response-defining thresholds, the sponsor
152 should specify how the change in drug use pattern will be measured. Certain changes in drug use
153 patterns, such as “fewer occasions of use per day” or “reduced amount of use per occasion,” may
154 prove impractical to measure. In addition, to support a drug use pattern as a response-defining
155 threshold, the sponsor should evaluate and submit evidence from clinical trials, longitudinal
156 observational studies, or other sources of information to show that such reduction in drug use
157 predicts clinical benefit (i.e., better health outcomes or psychosocial function). Sponsors should
158 discuss with the division approaches to measure change in drug use patterns and how evidence of
159 clinical benefit could be generated.

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162 **IV. OTHER OUTCOME MEASURES**

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164 FDA is interested in other outcome measures that sponsors might use to demonstrate clinical
165 benefit of medications for the treatment of OUD. There is great societal interest in assessing
166 additional, clinically meaningful endpoints such as reduction in hospitalizations, emergency
167 department visits, overdose, and death as well as improvements in the ability to resume work,
168 school, or other productive activity. FDA recognizes that evaluating these outcomes could
169 require larger trials than those usually conducted for marketing approval. However, the
170 collection of data on clinically meaningful outcomes would be highly valuable, and FDA
171 encourages sponsors to consider collecting such data even if not intended to support a regulatory
172 decision. Furthermore, the use of these outcomes as clinical trial endpoints could provide the
173 basis for inclusion in the FDA-approved labeling. *Retention in treatment* is not recommended as
174 a stand-alone endpoint. Many features of trial design can produce incentives to remain *in*

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175 *treatment* without accruing clinical benefit. If a sponsor plans to include novel endpoints in a
176 drug development program for the treatment of OUD, FDA strongly encourages the sponsor to
177 discuss such plans with the division early in the drug development process.
178