Stimulant Use Disorders: Developing Drugs for 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DRAFT GUIDANCE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)

October 2023
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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of stimulant use disorders.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's or Agency's) current recommendations regarding the overall development program and clinical trial designs for the development of drugs to support indications for treatment of moderate to severe cocaine use disorder, treatment of moderate to severe methamphetamine use disorder, or treatment of moderate to severe prescription stimulant use disorder.[3] This draft guidance is intended to serve as a focus for continued discussions among Center for Drug Evaluation and Research staff (particularly the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, or the division), pharmaceutical sponsors, the academic community, and the public.[4] This guidance does not address treatment of intoxication or poisoning with various stimulants or treatment of withdrawal from stimulants.

Because FDA has yet to approve any medication treatments for stimulant use disorder, this guidance reflects current recommendations based on a number of uncertainties about the best

[1] 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.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] FDA understands that sponsors may also wish to consider the development of drugs to support indications for treatment of mild stimulant use disorders, though given past experience, it may be particularly challenging to demonstrate treatment is effective in individuals with mild stimulant use disorders. There may also be practical and ethical concerns about identifying, recruiting, and enrolling subjects with mild stimulant use disorders if the benefit-risk balance of the specific drug being studied is not appropriate for an individual with a mild stimulant use disorder. However, we encourage sponsors to contact FDA if this is of interest.

[4] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of these drugs.

approaches for treating stimulant use disorder and the best approaches for evaluating responses to treatment. This guidance also incorporates lessons learned about approaches for evaluating responses to treatment that are unlikely to be successful. FDA is engaged in an ongoing process to learn more about stimulant use disorders and their treatments to provide the best possible advice to sponsors.[5] As the evidence supporting the development of drugs for stimulant use disorder treatment evolves, the recommendations in this guidance and any recommendations given to sponsors at milestone meetings may change.

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: HETEROGENEITY OF STIMULANT USE DISORDERS AND POPULATIONS

The *Diagnostic and Statistical Manual of Mental Disorders, 5th edition,* (DSM-5) has a single diagnosis, *stimulant use disorder*, defined as "a pattern of amphetamine-type substance, cocaine, or other stimulant use leading to clinically significant impairment or distress," ranging from mild to severe.[6] The definition lists various symptoms of impairment or distress, but notably, it does not include any criteria related to amount or frequency of stimulant use.[7]

The group of individuals meeting DSM-5 criteria for stimulant use disorder is very heterogeneous, with individuals using different stimulants in a range of different settings and for different reasons. This heterogeneity may contribute to the difficulty in identifying medications that are efficacious for the entire subset of patients diagnosed with cocaine use disorder or methamphetamine use disorder, and even more for all patients meeting the broader criteria for stimulant use disorder. Cocaine, methamphetamine, and other stimulants have different mechanisms and effects, and this may lead to differences in clinical presentation and responses to treatment.

[5] A public workshop hosted by the Reagan-Udall Foundation for the FDA in October 2021 brought together experts from the patient community, academia, clinical care, FDA, the National Institute on Drug Abuse, pharmaceutical companies, and health insurance payers. Those experts emphasized the need for continued investment in clinical research and for consensus around clinically meaningful and patient-centric endpoints for assessing treatments for stimulant use disorder. The report can be found on the foundation's website at https://reaganudall.org/programs/substance-use-disorders.

[6] American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Arlington, VA: American Psychiatric Association, 561.

[7] The DSM-5 stimulant use disorder diagnostic criteria are available on pages 561 to 562 of the manual, which is available at https://dsm.psychiatryonline.org/doi/epdf/10.1176/appi.books.9780890425596.

III. DEVELOPMENT PROGRAM

This section includes general considerations for development programs evaluating potential drug treatments for stimulant use disorder. FDA is open to discussing various approaches to address these considerations; sponsors should engage the division early in the drug development process.

A. Early Phase Development Considerations

To characterize the safety profile of the drug, sponsors should conduct first-in-human studies in healthy volunteers. In addition to general phase 1 safety and pharmacokinetic studies, sponsors should address the potential for interactions between the investigational drug and the relevant stimulant in subjects who are experienced in taking stimulants. Because stimulants have the potential for single-dose lethality, sponsors should establish that the investigational drug does not potentiate the toxicity of the stimulant (e.g., with adverse effects such as tachycardia, hypertension, and central nervous system (CNS) activation). It should be expected that the subject with stimulant use disorder may be exposed to both the investigational drug and the stimulant concurrently. For this reason, sponsors should ensure that there is no clinically relevant drug-stimulant interaction (either pharmacokinetic or enhancement of the pharmacodynamic or adverse effects of the stimulant leading to exaggerated adverse effects) early in drug development.

- If there is a predicted interaction that may lead to an adverse event based upon the investigational drug and the stimulant's mechanism of action, or if there are observations in nonclinical studies or phase 1 studies of the investigational drug alone (e.g., adrenergic-type observations, CNS activation, or lowered seizure threshold in animal toxicology studies) that suggest the potential for an interaction with the stimulant, animal toxicology interaction studies should precede clinical phase 1 interaction trials. These toxicology studies should address risks such as acute cardiovascular effects, lowering of seizure threshold, or other specific predicted effects.[8]

- If sponsors observe serious interactions leading to toxicity in nonclinical studies, or if sponsors observe potentially important adverse events likely resulting from an interaction in phase 1 trials, sponsors should consider discontinuing development or suspending development and assessing the benefit-risk of continued development. Depending on the pharmacology of the investigational drug, sponsors should design animal toxicology studies and (if appropriate) phase 1 clinical trials in stimulant-experienced subjects to carefully assess any potential drug effect that may enhance the stimulant's adverse effects (e.g., CNS activity, adrenergic activity including assessment of cardiovascular effects, seizure threshold).

[8] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

After completing investigational drug-stimulant interaction nonclinical studies, as appropriate, sponsors should conduct initial investigational drug-stimulant interaction human trials in subjects who are experienced with the stimulant through the route of administration of interest, who are not seeking treatment for their stimulant use disorders, and who are otherwise medically healthy. These trials should be conducted in carefully monitored situations where stimulant-associated adverse events can be managed. Sponsors should evaluate the effects of the investigational drug on the pharmacokinetics and pharmacodynamics (e.g., physiological effects) of the stimulant(s) of interest. These initial investigational drug-stimulant interaction human trials may also be able to provide some preliminary data on the ability of the investigational drug to modify subjective responses to the stimulant of interest. Additionally, FDA anticipates that the trials can provide information on how the investigational drug affects the detection of the stimulant in biological fluids. This is important in interpreting the results of toxicology tests that are used to detect illicit stimulant use in efficacy trials.

B. Efficacy Trial Considerations

1. Population

To improve the chances of success, we recommend that sponsors of drug development programs evaluating potential treatments for stimulant use disorder give careful attention to the populations they select for study. Thus, when evaluating the efficacy of a drug for the treatment of stimulant use disorder, the sponsor should consider studying people who use cocaine, methamphetamine, and prescription stimulants separately. Initial clinical trial evidence that therapeutic response is similar across different stimulants could provide useful information for later clinical trials with broader populations.

Some additional considerations for sponsors of drugs for the treatment of stimulant use disorders could include route of administration (oral, smoked, intravenous, or intranasal) and/or motivation for use of a specific stimulant (e.g., work performance enhancement, club drug use, escape, sensation seeking, sexual performance enhancement). Some subpopulations may be particularly responsive, or nonresponsive, to specific types of treatment. Another factor sponsors may want to consider is mechanism of action: Some drugs proposed to treat stimulant use disorder might be more suitable for helping subjects actively using stimulants, while other drugs might be more suitable for preventing relapse in subjects who are abstinent at baseline.

To increase the chance of matching the investigational drug to the population likely to benefit, we recommend that sponsors incorporate early-stage clinical trials that evaluate response in different stimulant use disorder populations. Based upon the results of the earlier trials, sponsors may determine whether it is appropriate to conduct later trials in broader populations or in narrower, more targeted ones. Note that sponsors should not need to study their drugs in all conceivable populations before submitting marketing applications. Sponsors are encouraged to contact the division to discuss the development of trials to ensure sufficient statistical power and sample size to adequately capture a representative segment of subjects with stimulant use disorder, while balancing the potential for success in matching the investigational drug to the population likely to benefit.

Finally, sponsors should enroll subjects whose primary problem is their stimulant use disorder. Some individuals who use stimulants report using them to manage other problems, not because of a particular urge or desire to use stimulants. For example, some patients with opioid use disorder report using methamphetamines to manage the effects of opioids (either to treat withdrawal or to prevent overdose). These individuals may meet diagnostic criteria for a stimulant use disorder but would be unlikely to respond to a drug that addressed only that problem, and thus FDA does not recommend that such subjects be included in trials of drug treatments for stimulant use disorder.

2. Design and Duration

Sponsors should conduct randomized, double-blind, and placebo-controlled efficacy trials. FDA strongly recommends sponsors provide behavioral treatment to all trial subjects and that the behavioral treatment be standardized and described in the protocol.

Trials should also be of sufficient duration to achieve a meaningful change in stimulant use behavior and/or stimulant use disorder symptoms and to demonstrate that this effect is durable. Improvement may not occur immediately, given the nature of stimulant use disorder, and for this reason sponsors could consider a scientifically justifiable portion of the trial duration a grace period for analytic purposes.[9] Because of the time period required to demonstrate a response to treatment, FDA typically recommends demonstrating improvement in the trial primary endpoint for 3 months or longer, which may involve a controlled period of 6 months of observation. FDA encourages sponsors to discuss any questions about trial duration, such as the characteristics of the specific study sample and the anticipated effect of the intervention, with the division.

3. Measurements of Drug Use

To bolster confidence in trial results, FDA suggests that sponsors propose and explain the rationale for a combination of self-report and biological testing. FDA's recommended considerations for each are as follows:

- **Self-report**: For any endpoint involving a pattern of stimulant use, a certain amount of reliance on self-report will likely be necessary. Sponsors can propose daily reports, staff-assisted *timeline followback* reconstruction at visits,[10] or other self-report tools. Because self-report can be subject to issues related to recall, response bias, social desirability, and other factors, self-report of drug use may not provide persuasive data by itself.

- **Biological testing:** FDA recognizes that biological testing is often an important component of monitoring response to treatment. However, FDA does not currently have

[9] Kiluk BD, Carroll KM, Duhig A, Falk DE, Kampman K, Lai S, Litten RZ, McCann DJ, Montoya ID, Preston KL, Skolnick P, Weisner C, Woody G, Chandler R, Detke MJ, Dunn K, Dworkin RH, Fertig J, Gewandter J, Moeller FG, and Strain EC, 2016, Measures of Outcome for Stimulant Trials: ACTTION Recommendations and Research Agenda, Drug Alcohol Depend, 158:1–7.

[10] *Timeline followback* is described on the National Institute on Drug Abuse Clinical Trials Network's Common Data Elements website at https://cde.drugabuse.gov/instrument/d89c8e23-16e5-625a-e040-bb89ad43465d.

evidence to support a recommendation on the optimal frequency of biological testing, including urine toxicology. Sponsors should consider expected effects and any impact of the investigational drug on the biological detection window, striking a balance between minimizing subject burden and providing some degree of biological confirmation of self-report.[11]

During nonclinical development or phase 1 trials, sponsors should determine any potential for the investigational drug to alter detection of the stimulant. This could occur for various reasons, including interference with the assay for the stimulant or because of a drug-stimulant interaction with alteration in metabolism or clearance of the stimulant. Sponsors should be aware that outcome measures based on detecting changes in day-to-day use, rather than more sustained periods of nonuse, must be carefully interpreted based upon a knowledge of the pharmacokinetics (detection in urine or other matrices) of the stimulant and any interactions between the investigational drug and the stimulant that alter urinary excretion of the stimulant or metabolites. Note that some treatment approaches for stimulant use disorder (e.g., immunotherapy such as a monoclonal antibody directed at the drug, a vaccine leading to antibody developed to the drug) may both markedly reduce free drug, increase bound drug, and prolong detectable urinary excretion. Trial designs, including the use of urine or biochemical testing in studies of such approaches, should be informed by such interactions.

4. Measurements of Drug Use to Assess Treatment Response

Historically, clinical trials of treatments for stimulant use disorder have focused on the results of urine toxicology testing as a way to assess response to treatment; and as noted above, FDA recognizes the importance of urine toxicology testing for this purpose. Urine toxicology results (e.g., in reflecting pattern of stimulant use) are a surrogate measure because they are not a reflection of how the subject feels, functions, or survives.[12] We have previously advised that a sustained period of negative urine toxicology findings, indicating abstinence, could be a valid surrogate for clinical benefit. However, FDA does not, and has not, advised that the only appropriate endpoint based on urine toxicology results is the number of subjects achieving complete abstinence.

FDA is open to other endpoints that reflect meaningful improvement in stimulant use disorder, noting that measuring other changes in pattern of stimulant use and establishing their clinical benefit may be more complex. For example, capturing periods of nonuse, such as number of

[11] Many previous trials of drugs to treat cocaine use disorder incorporated thrice-weekly toxicology testing based on prior trials in other addictive disorders. Quantitative assays were developed for the major metabolite of cocaine (benzoylecgonine) and an algorithm for distinguishing new use from previous use, minimizing false-positive urine tests caused by carryover when sampling thrice weekly. Less is known about the detection of methamphetamines or other stimulants in urine and other body fluids. However, prior research has suggested that thrice-weekly visits may be burdensome to subjects and, thus, contribute to missing data and trial drop out.

[12] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

days of nonuse per period (e.g., per week, per month), may be more practical. Conversely, there is consensus that certain changes in pattern of stimulant use, such as *fewer uses per day* or *reduced amount of drug used per occasion of use*, are impractical to measure.[13] They are also of uncertain significance when the stimulant used is illicit, and therefore of unknown and inherently variable potency. Thus, some changes in pattern of stimulant use are likely unsuitable as clinical trial endpoints. FDA encourages sponsors to discuss responder definition with the division.

Likewise, change from baseline analyses based on pattern of use is very challenging. It is not possible to get a *right now* baseline measurement of a pattern of stimulant use, the way one can for blood pressure or pain score, or a snapshot that captures the overall level of use over a period of time (analogous to hemoglobin A1c). However, the entry criteria may specify severity of use (e.g., moderate to severe cocaine use disorder), so use over time in the trial may be more useful than comparison to baseline, given the challenges of adequately evaluating the baseline.

C. Endpoints

The subsections below lay out considerations for change in pattern of stimulant use, change in disease status using diagnostic criteria, and other potential outcome assessments. Sponsors may consider demonstrating an effect in one or more of these options.

1. Change in Pattern of Stimulant Use

The term *pattern of stimulant use* refers to the frequency (days of use per week or month), timing, and intensity (uses per day or amount per use) of stimulant use by an individual subject. As discussed above, from a practical standpoint, intensity parameters are difficult to reliably measure, and frequency measures are more feasible to measure.

FDA prefers the phrase *change in pattern of stimulant use* (as opposed to the more ambiguous phrase *reduction in stimulant use*) and recommends its use to emphasize that within-subject responses are of interest. In practice, the proportion of subjects achieving a target pattern of use days per period of time could be an acceptable endpoint, with a prespecified target pattern of use that defines a relevant within-subject response. In contrast, evaluation of the difference between treatment groups in the mean number of days free of use is not recommended.

Sponsors should prespecify in the protocol a target pattern that reflects a satisfactory response to treatment for individual subjects, to be used to define a responder for the purposes of analysis. A trial to evaluate a treatment aimed at modifying the number of days per period of time should include a minimum frequency of use as an entry criterion, such that the target pattern represents improvement. Note that some individuals have a baseline pattern of infrequent binge use of a stimulant (e.g., cocaine use every several weeks); a study of such subjects would need to define a target pattern that reflects meaningful change for that pattern.

Although stimulant use patterns are not direct measures of how subjects feel or function, such assessments may be considered as candidate surrogate endpoints. Given the unmet medical need

[13] See footnote 9.

for stimulant use disorder medication treatments, a candidate surrogate or intermediate clinical endpoint may be appropriate based on the scientific support for that endpoint. Sponsors should explain their choice of a responder definition, ideally using data supporting the relationship of the target pattern to clinical benefit. This recommendation may not apply to sponsors proposing a prolonged period of nonuse as a target pattern because the benefit of this pattern can be assumed. It may be appropriate for the responder definition to incorporate allowances for a certain number of missing visits. It may also be appropriate to focus on the last several months of the treatment period, recognizing that treatment response may not occur right away.

To aid in interpretation of results, sponsors should provide a graph that shows the proportions of responders by treatment arm over the entire range of possible response definitions. Sponsors should also display results over time by presenting a summary measure (e.g., proportion of subjects by treatment group that meets response criteria) over the duration of the trial and by using methods that permit visualization of the progress of individual subjects over time.

Sponsors should consider the following caveat to using pattern of stimulant use as an outcome measure. Some types of treatment might prolong or potentiate stimulant effects such that subjects reduce use of the stimulant without reducing the subjective and rewarding effects, or reducing health harms of the stimulant use. In this scenario, reliance on pattern of stimulant use as an assessment of response to treatment may lack validity, and direct measures of clinical benefit would be more suitable.

2. Change in Disease Status Using Diagnostic Criteria

Sponsors should enroll trial subjects who meet DSM-5 criteria for moderate to severe stimulant use disorder at baseline, based on clinical interview. These criteria include a variety of symptoms and reflect how subjects feel and function. DSM-5 also provides a definition of remission to be used as a specifier. After criteria for stimulant use disorder were previously met, *early remission* is defined as meeting none of the criteria for stimulant use disorder for between 3 and 12 months, and *sustained remission* is defined as meeting none of the criteria for at least 12 months. Both definitions for remission contain an exception that the criterion for craving may continue to be met.[14]

A suitable primary endpoint could be the proportion of subjects meeting criteria for early remission from stimulant use disorder at the end of the trial.

We do not recommend using change in the number of DSM-5 diagnostic criteria endorsed. Although this may seem to be an appropriate way to detect changes in the severity of stimulant use disorder, this approach has several concerns. The DSM-5 is intended as a diagnostic instrument, not a method of monitoring response to treatment. The presence or absence of many criteria is determined based on an interviewer's judgment of whether the problem occurs often, frequently, persistently, or recurrently. The frequency or intensity of symptoms may increase or decrease without the number of criteria changing; one symptom may resolve while another appears; or, potentially, several symptoms may resolve but a more concerning one may arise,

[14] American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Arlington, VA: American Psychiatric Association, 562.

yielding a misleading appearance of improvement. For these reasons, FDA strongly encourages sponsors interested in using endpoints reflecting disease severity to select, modify, or develop suitable instruments (see section III.C.3., Use of Other Clinical Outcome Assessments).

3. Use of Other Clinical Outcome Assessments

Using input from patients, family members, and/or clinicians to determine the most concerning symptoms or experiences associated with stimulant use disorder, sponsors could develop a clinical outcome assessment (e.g., a patient-, observer-, or clinician-reported outcome measure to evaluate a direct effect on how patients feel or function). A suitably developed, fit-for-purpose measure that assesses relevant aspects of a subject's health status, functioning, and/or symptoms may be appropriate as a primary endpoint for a clinical trial and may be the most suitable approach for some investigational drugs.

FDA is also aware of interest in stimulant craving (usually defined as a strong desire or wish to use stimulants) as a potential target for treatment. Craving has not been consistently defined or understood, but it is viewed as a significant source of distress for patients and could be a suitable target for treatment. FDA encourages the development of a suitably developed, fit-for-purpose measure of craving and envisions incorporating claims about effects on craving as secondary endpoints for drugs that are effective treatments for stimulant use disorder. We are also open to data demonstrating the ability of craving modification to predict clinical benefit to consider craving as a potential primary endpoint.

We encourage sponsors to evaluate the effect of drugs in development for stimulant use disorder on various adverse clinical outcomes. Examples of meaningful outcomes may include reduced overall or overdose mortality or fewer hospitalizations. Similarly, FDA is interested in outcome measures that sponsors might use to demonstrate clinical benefit of investigational drugs for treating stimulant use disorder such as improvements in the ability to resume work, school, or other productive activity or fewer encounters with the criminal justice system. We are open to a well-designed, appropriately justified composite endpoint, as described in the guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022).[15]

FDA recognizes that evaluating these outcomes could require larger trials than those usually conducted for marketing approval. However, collecting data on clinically meaningful outcomes even if not intended as primary support for a regulatory decision would be highly valuable, and FDA encourages sponsors to consider collecting such data. Furthermore, using these outcomes as clinical trial endpoints may help to validate endpoints that may be considered for use in clinical trials in the future. 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 stimulant use disorder, FDA strongly encourages the sponsor to discuss such plans with the division early in the drug development process.

[15] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

IV. BENEFIT-RISK CONSIDERATIONS

When selecting an endpoint to demonstrate efficacy for a specific drug, sponsors should consider that, ultimately, the demonstrated benefit of a drug will be weighed against the risk under FDA's drug approval standard (section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d))).[16] Uncertainties regarding benefits and risks are considered when making an approval determination; a drug with greater risks may require a greater magnitude and certainty of benefit to support approval.[17] If the drug itself has abuse potential,[18] FDA may consider the public health effects of the drug as part of the overall benefit-risk assessment, including the drug's potential effect on risks to both patients and nonpatients, such as members of the patient's household (e.g., children, visitors). The risks considered may include those related to misuse,[19] abuse, stimulant use disorder, overdose, and accidental exposures, particularly in children.[20]

V. LABELING

Regardless of the outcome measure chosen, a drug that has been determined to be safe and effective could be indicated for the "treatment of [specific drug] use disorder" and modified by the level of severity studied (e.g., "moderate to severe methamphetamine use disorder").

FDA envisions that the indication would generally mirror the studied population (potentially including the stimulant route(s) of administration for the studied population);[21] however, the labeled population is determined based upon the results of the clinical program that may support use in a broader or narrower population than was studied.[22] It is possible that a drug with

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[16] See also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*.

[17] See footnote 16.

[18] As used in this guidance, the term *abuse* refers to the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.

[19] As used in this guidance, the term *misuse* refers to the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed.

[20] See the draft guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (September 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[21] See the draft guidance for industry *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials* (April 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[22] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

clinical trials finding efficacy and safety in multiple populations using different stimulants, in different contexts, by different routes, could be approved for a broad indication for the treatment of stimulant use disorder. An *all-comers* trial could theoretically support such a broad indication if it were convincingly positive in all subgroups, but the size of a trial needed to support such a conclusion could likely make it less practical than studying groups separately.

VI. EXPEDITED PROGRAMS

FDA encourages the development of treatments for stimulant use disorder and novel trial designs. Stimulant use disorder development programs may be eligible for one or more of FDA's expedited programs, as applicable. FDA encourages early discussion of drugs that could treat stimulant use disorder and may be eligible for expedited programs.

These expedited programs and their relevant criteria are described in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). Potentially applicable expedited programs include fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval. Although each program differs, they all offer some form of expedited review and guidance for sponsors of drug development programs for serious or life-threatening conditions to address unmet medical need.