Major Depressive Disorder: 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DRAFT GUIDANCE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
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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the monotherapeutic, combination, and adjunctive treatment of major depressive disorder (MDD).[2] Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs for antidepressant drug products. This draft guidance is intended to serve as a focus for continued discussions among the Division of Psychiatry Products (the Division), pharmaceutical sponsors, the academic community, and the public.[3]

This guidance does not address bipolar depression. This guidance also does not address the development of nonpharmacologic treatments for depression.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

[1] This guidance has been prepared by the Division of Psychiatry Products 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 therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of antidepressant drug products.

[4] 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.

This guidance revises the guidance for industry *Guidelines for the Clinical Evaluation of Antidepressant Drugs* issued in September 1977. Major revisions were made to the 1977 guidance to align it with the FDA's current thinking on this topic. After it has been finalized, this guidance will replace the 1977 guidance.

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

MDD is a debilitating and chronic illness. According to a 2018 World Health Organization (WHO) Fact Sheet, depression is a "common illness worldwide, with more than 300 million people affected."[5]

The symptoms of MDD are defined in the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM).[6] The DSM also lists several other depressive disorders distinguished by differences in severity, chronicity, etiology, and time course of symptoms. Although this guidance focuses on MDD, some of the principles described here may be applicable to clinical trials of drugs intended to treat other forms of depression. Sponsors should seek FDA feedback on development programs for non-MDD depression treatments.

III. DEVELOPMENT PROGRAM

A. General Considerations

Traditional clinical trial designs for antidepressant drugs have been based on an expected 4- to 8-week onset of action. All conventional classes of antidepressants have been oral medications for chronic daily administration, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin-reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and others. Their FDA-approved indications have included treatment of MDD (in adult and pediatric patients), adjunctive therapy to existing MDD treatment, and treatment-resistant depression.

MDD treatment indications may be divided into two phases: short-term (i.e., treatment of a depressive episode) and maintenance (i.e., relapse prevention). The regulatory issues for these phases depend on the particular characteristics of each antidepressant.

[5] WHO, 2018, Depression Fact Sheet, accessed April 10, 2018, http://www.who.int/mediacentre/factsheets/fs369/en/.

[6] American Psychiatric Association, editor, 2013, Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

Rapid-acting antidepressant drugs are in development, and their clinical trial design issues and regulatory considerations may differ from those of previously approved antidepressant drugs, which generally take 4 to 6 weeks to show their effect.

B. General Pharmacological and Clinical Safety Considerations

1. Nonclinical Safety Considerations

In addition to the usual animal toxicology studies needed for any new molecular entity, sponsors should consider the drug's intended duration of treatment, mechanism of action, and known pharmacodynamic and/or pharmacokinetic interactions with other coadministered drugs when determining the types of nonclinical safety studies needed. As sponsors explore drugs with new mechanisms of action, they should be aware that there could be specific nonclinical safety studies needed based on mechanism-specific concerns.

For example, N-methyl-d-aspartate (NMDA) receptor antagonists have been found to cause Olney lesions, which are vacuoles that may precede the onset of permanent injury in the form of neuronal cell death in the brain. For the NMDA receptor antagonist drug class, a study evaluating the acute neurotoxic effect of the drug is expected before the first human use. The protocol for this study should be submitted for review and feedback before initiating the study.

We recommend that all general toxicology studies contain a thorough histopathology evaluation of at least seven slices of the brain as described in Bolon et al., 2013.[7] Use of alternate slices can be justified based on the predicted sensitivity of the drug. If the drug is intended for chronic use, the duration of nonclinical studies should conform to the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*. Sponsors are encouraged to request a pre-investigational new drug application meeting with the FDA to discuss the specific requirements of the nonclinical program and the need for special toxicity studies.

2. Clinical Pharmacology Considerations

Characterization of a drug's pharmacokinetics and pharmacodynamics in early phase development is critical to assist identification of rational doses and dosing intervals for the phase 3 trials, and to develop drug switching strategies. Different types of antidepressants, such as the rapid-acting drugs under development, are likely to have different pharmacokinetic and pharmacodynamic properties that may involve specific studies and methods of analysis.

For all antidepressants, sponsors should conduct pharmacodynamic studies, such as in vivo receptor binding studies or biomarker studies, to initially identify appropriate dosage ranges, and these should be followed by clinical endpoint dose-response studies. Sponsors generally should include at least one dose-finding trial using a fixed-dose design with at least three doses.

[7] Bolon, B, et al., 2013, STP Position Paper: Recommended Practices for Sampling and Processing the Nervous System (Brain, Spinal Cord, Nerve, and Eye) During Nonclinical General Toxicity Studies, Toxicol Pathol, 41, 1028–1048.

Sponsors can apply dose-response or exposure-response modeling and simulation to integrate the information obtained in early phase clinical trials and to inform dosing regimen selection for phase 3 trials.

To develop an antidepressant intended for adjunctive therapy, early assessment of pharmacokinetic interaction with the background therapy is highly recommended.

C. Specific Efficacy Trial Considerations

Sponsors should consider the following recommendations concerning study design, study population criteria, efficacy endpoints, statistical considerations, and safety considerations.

1. Study Design

a. Short-term treatment of a depressive episode

- **Choice of control group —** Substantial responses are typically seen in placebo groups in antidepressant trials, and these are often larger than the drug-placebo difference. For that reason, trials of effective antidepressants have a high failure rate (about 50 percent). Therefore, it is not possible to identify a consistent drug effect that could be used as a noninferiority margin in comparative trials. A placebo group is necessary to ensure that observed effects are not the result of spontaneous improvement, expectation bias, attention from health care professionals involved in the trial, regression to the mean, or other factors not related to the activity of the study drug. Randomized, double-blind, placebo-controlled, parallel designs are the current standard for short-term efficacy trials in MDD. A substantially earlier or larger effect could be demonstrated in an active-control superiority trial.

- **Timing of effect —** Study duration and timing of assessment of primary endpoints depends on the mechanism of action of the antidepressant and the expected onset of the treatment effect. Antidepressants in established classes (e.g., SSRIs, SNRIs) typically need studies of 6 to 8 weeks duration to demonstrate efficacy, with the effect first appearing after 3 to 4 weeks. Thus, we consider 6 to 8 weeks an appropriate study duration for short-term efficacy endpoints for these types of antidepressants.

  For rapid-acting antidepressants, the timing of effect considerations include the following:

  – Efficacy generally should be demonstrated within 1 week for a rapid-acting antidepressant. Some novel antidepressants are thought to be effective within hours or days. In such cases, an earlier primary efficacy endpoint would be appropriate.

  – Durability of effect beyond the initial response should be characterized. To demonstrate both early onset of action and durability of effect, a primary efficacy endpoint early in the course of treatment would be chosen, with continued observation of drug-placebo differences over time. The precise studies depend on

how the drug is intended to be used, for example as a predecessor to a conventional antidepressant or as a drug for repeated use. In the latter case, the appropriate dosing interval could be determined by randomizing, after the initial dose, to several different dosing intervals.

Sponsors planning to employ novel trial designs should request a meeting with the FDA and seek early advice on relevant trial design and statistical considerations.

b. Maintenance treatment

Because depression usually is a cyclical disease, maintenance studies of conventional antidepressants are actually assessments of the ability of the drug to reduce the rate of recurrence of depression. Thus, typical studies generally should be at least 6 months in duration, as most recurrences are delayed. To inform labeling regarding maintenance treatment, after approval of an antidepressant, the FDA typically requests a postmarketing commitment to conduct a double-blind randomized withdrawal trial. To date, such trials have included an open-label stabilization period followed by randomization to either continued treatment or to placebo. For rapid-acting antidepressants, there is interest in whether the rapid effect does in fact persist for the episode treated. Demonstration of maintenance effects usually has different study requirements depending on the drug's dosing schedule, long-term safety considerations, and whether long-term usage is feasible. In general, long-term safety assessments should be incorporated in the design of maintenance studies (see section III.C.5., Phase 3 or 4 (Postmarketing) Safety Considerations).

The FDA is interested in studies that explore whether treatment response can be maintained with a lower dose of the drug than is needed for short-term efficacy, and whether a lower dose may improve tolerability. We may consider the results of such studies for labeling.

Of note, randomized withdrawal studies provide a useful opportunity to assess whether a treatment is associated with a discontinuation syndrome. Sponsors should systematically assess adverse events that occur upon drug discontinuation.

c. Noninferiority design

As noted above, noninferiority designs are not able to establish efficacy for antidepressants. High placebo response rates and small magnitude of treatment effect (relative to placebo) are of concern in most conventional antidepressant trials, which makes defining the active control effect and choosing a noninferiority margin difficult.

d. Partial response and treatment-resistant depression

Although it is reasonable to distinguish between adjunctive therapy for partial responders versus monotherapy for nonresponders based on intended use, the distinction is somewhat arbitrary. Response, partial response, and nonresponse exist on a continuum with no universally accepted definitions or cut points for differentiation. Nevertheless, we distinguish between these conditions in considering indications for labeling, and the types of studies needed to demonstrate

efficacy in adjunctive therapy versus treatment-resistant depression (TRD) are quite different. For adjunctive treatment, studies should include patients with partial responses to other antidepressant therapies; the investigational drug should be compared to placebo when added to the baseline antidepressant. Patients who have not responded to more than one prior antidepressant, administered at an adequate dose and duration, should be enrolled in TRD studies. Patients should be randomized to either the new treatment or to continue the antidepressant to which they had failed to respond.

Sponsors are encouraged to discuss their proposed study designs with the FDA before initiating trials intended to support a marketing application.

2. Study Population and Entry Criteria

Trials designed to assess the efficacy of antidepressant drugs should include patients with DSM-defined MDD. The diagnosis should be confirmed via a semi-structured interview such as the current Structured Clinical Interview for DSM or MINI International Neuropsychiatric Interview.

Study populations should reflect a range of severities of MDD, although trials to date in patients with less-than-moderate depression have not been successful. Investigators should seek demographically broad populations and avoid unnecessary restriction of study populations (e.g., by excluding patients with concomitant illness and concomitant therapy (although known or anticipated drug-drug interactions should be avoided)). Patients with a history of suicidal ideation and behavior need not be systematically excluded from trials. See also section III.C.6., Additional Considerations for Special Populations. Sponsors should provide the rationale for restrictive inclusion and exclusion criteria.

3. Selection and Adjudication of Efficacy Endpoints

Clinician-rated outcome measures are the current standard for assessing efficacy in antidepressant trials. To date, the FDA has accepted the following as primary endpoints in phase 3 studies to support an MDD indication:

- Hamilton Depression Rating Scale (typically the 17-item version)
- Montgomery Asberg Depression Rating Scale
- Children's Depression Rating Scale

Other primary endpoints may be acceptable; however, sponsors planning to use a novel primary endpoint in phase 3 trials should seek advice before initiating studies.

Secondary endpoints assess other domains of symptom improvement relevant for labeling. Common endpoints for consideration include:

- Clinical Global Impression (CGI)
- Sheehan Disability Scale

In the past, either CGI-Improvement (CGI-I) measured at the end of study or CGI-Severity (CGI-S) assessed as change from baseline have been acceptable. However, the Division prefers CGI-S to CGI-I, given the potential influence of recall bias on CGI-I.

4. Statistical Considerations

Because of high placebo response and dropout rates that are commonly observed, sponsors should consider these factors in sample size calculations to ensure that the trial has sufficient statistical power to detect the anticipated treatment effect. In general, a detailed statistical analysis plan should be submitted before trial initiation to obtain timely feedback on the trial design and statistical concerns. Any consideration of nontraditional designs or novel analyses should be preceded by a meeting with the FDA to review and reach agreement on the plan. Sponsors who submit the statistical analysis plan after enrollment of the first patient (but before data lock) should provide documentation that the analysis plan was not developed or altered with efficacy data in hand.

5. Phase 3 or 4 (Postmarketing) Safety Considerations

a. Long-term safety data

Conventional drugs for treatment of MDD are often taken long-term (defined as continuous or intermittent use for at least 6 months), given that MDD is a chronic condition requiring ongoing management to reduce the rate of recurrence. Therefore, the safety database should meet the patient exposures outlined in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Note that these are minimum patient exposures and that larger exposures may be needed for specific drugs depending on safety concerns identified during drug development.

b. Pregnancy

Given that pregnant women typically are excluded from antidepressant trials but remain a population that sometimes requires depression treatment, sponsors should collect safety data in women who are inadvertently exposed in pregnancy during drug development trials and in pregnant women who use these drugs in the postmarketing setting. Sponsors should use existing antidepressant pregnancy registries (e.g., National Pregnancy Registry for Psychiatric Medications) or establish their own registry.

6. Additional Considerations for Special Populations

a. Pediatrics

At present, data are insufficient to support extrapolation of adult efficacy data to support efficacy in pediatric MDD because pediatric studies of antidepressants effective in adults have frequently been unsuccessful. Even for antidepressants already approved in adult MDD, to obtain an initial short-term efficacy indication in pediatric MDD sponsors should conduct two independent,

adequate and well-controlled clinical trials in pediatric patients, in addition to pharmacokinetic and safety information in the relevant pediatric age groups. The Division may consider reliance on positive adult maintenance studies for a maintenance indication study waiver after studies have established short-term efficacy and long-term safety in the pediatric population.

For pediatric MDD, we consider the relevant age groups to be children (ages 7 through 12) and adolescents (ages 13 through 17). We consider these age groups to be unique populations with their own specific needs (e.g., different developmental physiology, different psychosocial concerns). Therefore, the traditional pediatric development program should consist of pharmacokinetic, efficacy, and safety studies that cover both age groups. For patients aged 0 to 6 years, including neonates, studies are considered impossible or highly impractical because of the low prevalence of MDD in this age range, and a study waiver is generally granted. Supplementary juvenile animal studies may be needed before the initiation of drug treatment in pediatric patients. Protocols for clinical and nonclinical studies should be submitted for review and feedback before initiating the study.

b. Other special populations

Geriatric patients and patients with renal insufficiency, cardiac disease, chronic pain, and hepatic impairment should be included in trials during drug development, if feasible. Because patients with human immunodeficiency virus and hepatitis C can require treatment with antidepressants, these patients should not be excluded from trials during drug development. Patients with a history of substance abuse should also be considered for inclusion in these studies, although such inclusions should be weighed against concerns about diagnostic and medication effect confounders, including substance abuse maintenance therapy. Accordingly, patients whose substance use disorder is not at least in partial remission will likely be excluded from antidepressant trials depending on the level of particular confounding concerns.

D. Biomarker Considerations

At present, there are no surrogate markers for assessment of antidepressant effectiveness. Biomarkers could be developed for disease subtyping, monitoring of disease progression, dose selection, and prediction of treatment response. Sponsors seeking to include a biomarker in their clinical trials should request a guidance meeting with the Division early in the development program.