
Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Javier Muñiz, Jean Kim, or Juliette Touré at 301-796-2260.

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

**June 2018
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Revision 1

Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry

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Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry¹

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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 This draft guidance is intended to serve as a focus for continued discussions among the Division of Psychiatry Products (the Division), pharmaceutical sponsors, the academic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>.

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

39
40 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
41 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
42 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
43 the word *should* in Agency guidances means that something is suggested or recommended, but
44 not required.

45
46

II. BACKGROUND

47
48

49 MDD is a debilitating and chronic illness. According to a 2018 World Health Organization
50 (WHO) Fact Sheet, depression is a “common illness worldwide, with more than 300 million
51 people affected.”⁵

52

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

59

60

III. DEVELOPMENT PROGRAM

61
62

A. General Considerations

63
64

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

72

73 MDD treatment indications may be divided into two phases: short-term (i.e., treatment of a
74 depressive episode) and maintenance (i.e., relapse prevention). The regulatory issues for these
75 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.

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76
77 Rapid-acting antidepressant drugs are in development, and their clinical trial design issues and
78 regulatory considerations may differ from those of previously approved antidepressant drugs,
79 which generally take 4 to 6 weeks to show their effect.

80
81 **B. General Pharmacological and Clinical Safety Considerations**

82
83 *1. Nonclinical Safety Considerations*

84
85 In addition to the usual animal toxicology studies needed for any new molecular entity, sponsors
86 should consider the drug's intended duration of treatment, mechanism of action, and known
87 pharmacodynamic and/or pharmacokinetic interactions with other coadministered drugs when
88 determining the types of nonclinical safety studies needed. As sponsors explore drugs with new
89 mechanisms of action, they should be aware that there could be specific nonclinical safety
90 studies needed based on mechanism-specific concerns.

91
92 For example, N-methyl-d-aspartate (NMDA) receptor antagonists have been found to cause
93 Olney lesions, which are vacuoles that may precede the onset of permanent injury in the form of
94 neuronal cell death in the brain. For the NMDA receptor antagonist drug class, a study
95 evaluating the acute neurotoxic effect of the drug is expected before the first human use. The
96 protocol for this study should be submitted for review and feedback before initiating the study.

97
98 We recommend that all general toxicology studies contain a thorough histopathology evaluation
99 of at least seven slices of the brain as described in Bolon et al., 2013.⁷ Use of alternate slices can
100 be justified based on the predicted sensitivity of the drug. If the drug is intended for chronic use,
101 the duration of nonclinical studies should conform to the ICH guidance for industry *M3(R2)*
102 *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing*
103 *Authorization for Pharmaceuticals*. Sponsors are encouraged to request a pre-investigational
104 new drug application meeting with the FDA to discuss the specific requirements of the
105 nonclinical program and the need for special toxicity studies.

106
107 *2. Clinical Pharmacology Considerations*

108
109 Characterization of a drug's pharmacokinetics and pharmacodynamics in early phase
110 development is critical to assist identification of rational doses and dosing intervals for the phase
111 3 trials, and to develop drug switching strategies. Different types of antidepressants, such as the
112 rapid-acting drugs under development, are likely to have different pharmacokinetic and
113 pharmacodynamic properties that may involve specific studies and methods of analysis.

114
115 For all antidepressants, sponsors should conduct pharmacodynamic studies, such as in vivo
116 receptor binding studies or biomarker studies, to initially identify appropriate dosage ranges, and
117 these should be followed by clinical endpoint dose-response studies. Sponsors generally should
118 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.

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

122

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

125

126 **C. Specific Efficacy Trial Considerations**

127

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

130

131 *I. Study Design*

132

133 *a. Short-term treatment of a depressive episode*

134

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

146

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

153

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

156

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

160

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

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

169
170 Sponsors planning to employ novel trial designs should request a meeting with the FDA
171 and seek early advice on relevant trial design and statistical considerations.

172 173 b. Maintenance treatment

174
175 Because depression usually is a cyclical disease, maintenance studies of conventional
176 antidepressants are actually assessments of the ability of the drug to reduce the rate of recurrence
177 of depression. Thus, typical studies generally should be at least 6 months in duration, as most
178 recurrences are delayed. To inform labeling regarding maintenance treatment, after approval of
179 an antidepressant, the FDA typically requests a postmarketing commitment to conduct a double-
180 blind randomized withdrawal trial. To date, such trials have included an open-label stabilization
181 period followed by randomization to either continued treatment or to placebo. For rapid-acting
182 antidepressants, there is interest in whether the rapid effect does in fact persist for the episode
183 treated. Demonstration of maintenance effects usually has different study requirements
184 depending on the drug's dosing schedule, long-term safety considerations, and whether long-
185 term usage is feasible. In general, long-term safety assessments should be incorporated in the
186 design of maintenance studies (see section III.C.5., Phase 3 or 4 (Postmarketing) Safety
187 Considerations).

188
189 The FDA is interested in studies that explore whether treatment response can be maintained with
190 a lower dose of the drug than is needed for short-term efficacy, and whether a lower dose may
191 improve tolerability. We may consider the results of such studies for labeling.

192
193 Of note, randomized withdrawal studies provide a useful opportunity to assess whether a
194 treatment is associated with a discontinuation syndrome. Sponsors should systematically assess
195 adverse events that occur upon drug discontinuation.

196 197 c. Noninferiority design

198
199 As noted above, noninferiority designs are not able to establish efficacy for antidepressants.
200 High placebo response rates and small magnitude of treatment effect (relative to placebo) are of
201 concern in most conventional antidepressant trials, which makes defining the active control
202 effect and choosing a noninferiority margin difficult.

203 204 d. Partial response and treatment-resistant depression

205
206 Although it is reasonable to distinguish between adjunctive therapy for partial responders versus
207 monotherapy for nonresponders based on intended use, the distinction is somewhat arbitrary.
208 Response, partial response, and nonresponse exist on a continuum with no universally accepted
209 definitions or cut points for differentiation. Nevertheless, we distinguish between these
210 conditions in considering indications for labeling, and the types of studies needed to demonstrate

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

218
219 Sponsors are encouraged to discuss their proposed study designs with the FDA before initiating
220 trials intended to support a marketing application.

221 222 2. *Study Population and Entry Criteria*

223
224 Trials designed to assess the efficacy of antidepressant drugs should include patients with DSM-
225 defined MDD. The diagnosis should be confirmed via a semi-structured interview such as the
226 current Structured Clinical Interview for DSM or MINI International Neuropsychiatric
227 Interview.

228
229 Study populations should reflect a range of severities of MDD, although trials to date in patients
230 with less-than-moderate depression have not been successful. Investigators should seek
231 demographically broad populations and avoid unnecessary restriction of study populations (e.g.,
232 by excluding patients with concomitant illness and concomitant therapy (although known or
233 anticipated drug-drug interactions should be avoided)). Patients with a history of suicidal
234 ideation and behavior need not be systematically excluded from trials. See also section III.C.6.,
235 Additional Considerations for Special Populations. Sponsors should provide the rationale for
236 restrictive inclusion and exclusion criteria.

237 238 3. *Selection and Adjudication of Efficacy Endpoints*

239
240 Clinician-rated outcome measures are the current standard for assessing efficacy in
241 antidepressant trials. To date, the FDA has accepted the following as primary endpoints in phase
242 3 studies to support an MDD indication:

- 243
244
- 245 • Hamilton Depression Rating Scale (typically the 17-item version)
 - 246 • Montgomery Asberg Depression Rating Scale
 - 247 • Children's Depression Rating Scale

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

250
251 Secondary endpoints assess other domains of symptom improvement relevant for labeling.
252 Common endpoints for consideration include:

- 253
254
- 255 • Clinical Global Impression (CGI)
 - 256 • Sheehan Disability Scale

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

260

261 4. *Statistical Considerations*

262

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

272

273 5. *Phase 3 or 4 (Postmarketing) Safety Considerations*

274

275 a. Long-term safety data

276

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

285

286 b. Pregnancy

287

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

294

295 6. *Additional Considerations for Special Populations*

296

297 a. Pediatrics

298

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

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303 adequate and well-controlled clinical trials in pediatric patients, in addition to pharmacokinetic
304 and safety information in the relevant pediatric age groups. The Division may consider reliance
305 on positive adult maintenance studies for a maintenance indication study waiver after studies
306 have established short-term efficacy and long-term safety in the pediatric population.
307

308 For pediatric MDD, we consider the relevant age groups to be children (ages 7 through 12) and
309 adolescents (ages 13 through 17). We consider these age groups to be unique populations with
310 their own specific needs (e.g., different developmental physiology, different psychosocial
311 concerns). Therefore, the traditional pediatric development program should consist of
312 pharmacokinetic, efficacy, and safety studies that cover both age groups. For patients aged 0 to
313 6 years, including neonates, studies are considered impossible or highly impractical because of
314 the low prevalence of MDD in this age range, and a study waiver is generally granted.
315 Supplementary juvenile animal studies may be needed before the initiation of drug treatment in
316 pediatric patients. Protocols for clinical and nonclinical studies should be submitted for review
317 and feedback before initiating the study.
318

b. Other special populations

319
320
321 Geriatric patients and patients with renal insufficiency, cardiac disease, chronic pain, and hepatic
322 impairment should be included in trials during drug development, if feasible. Because patients
323 with human immunodeficiency virus and hepatitis C can require treatment with antidepressants,
324 these patients should not be excluded from trials during drug development. Patients with a
325 history of substance abuse should also be considered for inclusion in these studies, although such
326 inclusions should be weighed against concerns about diagnostic and medication effect
327 confounders, including substance abuse maintenance therapy. Accordingly, patients whose
328 substance use disorder is not at least in partial remission will likely be excluded from
329 antidepressant trials depending on the level of particular confounding concerns.
330

D. Biomarker Considerations

331
332
333 At present, there are no surrogate markers for assessment of antidepressant effectiveness.
334 Biomarkers could be developed for disease subtyping, monitoring of disease progression, dose
335 selection, and prediction of treatment response. Sponsors seeking to include a biomarker in their
336 clinical trials should request a guidance meeting with the Division early in the development
337 program.