August 17, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No.FDA-2018-D-1919: "Major Depressive Disorder: Developing Drugs for Treatment: Draft Guidance for Industry."

Dear Sir or Madam:

Takeda Pharmaceuticals U.S.A., Inc. (Takeda) appreciates the opportunity to comment on the Food and Drug Administration Draft Guidance: Major Depressive Disorder: Developing Drugs for Treatment. Takeda is a global research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda is focused in the therapeutic areas of oncology, gastroenterology, neuroscience and vaccines.

Takeda commends FDA's effort to update the guidance with FDA's current thinking to inform development of new antidepressants for patients. Takeda is committed to developing therapeutics for neuroscience disorders including depression and would like to provide recommendations to ensure the guidance is as informative as possible.

I. General Comments

Treatment-Resistant Depression

Because of the unmet need for therapies for treatment-resistant depression (TRD), Takeda recommends flexibility to design clinical trials for this patient population and not restrict them to monotherapy. For consistency with the American Psychiatric Association clinical practice guidelines[1] and to provide additional treatment options, when appropriate patients with TRD should be included in clinical studies investigating adjunctive or combination therapies if such studies were properly designed and scientifically sound to determine if there is a synergistic effect.

In addition, it is becoming increasingly common for sub-anesthetic doses of ketamine to be utilized for TRD in clinical practice, although the drug is not indicated for this use. The draft guidance should provide recommendations to demonstrate maintenance treatment of an antidepressant following initial dosing and immediate induction of treatment response from ketamine.

Digital Technology

Digital health technologies are being used to collect real world patient data so it would be helpful for the FDA to provide guidance. The draft guidance should provide specific recommendations to develop and

[1] American Psychiatric Association. (2010). *Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition*. Retrieved from https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

use digital technologies to collect patient data in clinical trials that can be used in regulatory decision-making and labeling.

Additional Labeling Claims

Takeda recommends the draft guidance addresses development strategies for an antidepressant to demonstrate an effect on specific symptoms (e.g. cognitive dysfunction, anhedonia) or reduced liability of a common adverse events (e.g. treatment-emergent sexual dysfunction (TESD), somnolence/insomnia, discontinuation symptoms).

II. Conclusions

Takeda appreciates the opportunity to comment on the Draft Guidance on Major Depressive Disorder: Developing Drugs for Treatment. Please find additional detailed comments in the table that follows. We would be happy to clarify our comments as needed.

Sincerely,

Janet Vessotskie
Sr. Director, Global Regulatory Intelligence & Policy
Takeda Pharmaceuticals U.S.A., Inc.

Specific Comments

Line #	Guidance Text	Comment/Recommendation
Lines 115-118	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.	The required inclusion of 3 or more active arms as per this draft guidance increases the potential for placebo response, as patients would know that they have </= 25% chance on being on placebo (expectation bias). The guidance should specify the need for dose-finding without specifying the required number of dose arms.
Lines 189-191	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	The guidance should clarify whether appropriate evidence that a lower dose improves

	efficacy, and whether a lower dose may improve tolerability. We may consider the results of such studies for labeling.	tolerability without compromising the maintenance response can be accomplished with either fixed dosing or flexible dosing study designs.
Lines 233-236	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.	The FDA should clarify the potential for a labeling claim if stratification of the subpopulation and appropriate analyses demonstrated a beneficial response.
Lines 299-306	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.	Historically, clinical trials in MDD pediatric patients required an active comparator control, however the draft guidance specifies a need for "adequate and well-controlled clinical trials in pediatric patients". The draft guidance should clarify if placebo-controlled study designs are acceptable.

Janssen Research & Development, LLC
Global Regulatory Affairs

17 August 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-D-1919: Major Depressive Disorder: Developing Drugs for Treatment: Draft Guidance for Industry; Availability, 83 Fed. Reg. 28851 (June 21, 2018)

Dear Sir or Madam:

Janssen Research & Development, L.L.C. (Janssen), a pharmaceutical company of Johnson & Johnson, appreciates the opportunity to provide comments on the Draft Guidance for Industry released by the Food and Drug Administration (FDA or the Agency), entitled "Major Depressive Disorder: Developing Drugs for Treatment (Draft Guidance),[1] which outlines the Agency's proposed approach to developing drugs for the treatment of major depressive disorder.

At Janssen, mood disorders, including depression, treatment-resistant depression and bipolar disorder, are an area of focus of our research. Our goal is to develop novel therapeutic agents that have fast onset of action, good safety and tolerability profiles, and that address common co-morbidities (for example, anxiety). We are developing several compounds for the treatment of mood disorders including, esketamine (a glutamate receptor modulator), for treatment-resistant depression and for major depressive disorder in patients at imminent risk for suicide.

Janssen would like to take this opportunity to thank the Agency for allowing comments to the June 2018 Draft Guidance and to offer the following general comments; additional specific comments are provided in the attached table:

- The Draft Guidance, is written at a high level, emphasizing that sponsors should seek advice from the Agency early on study designs and statistical considerations. Clinical development in depression continues to suffer from high failure rates due to high placebo responses and intra-/inter-subject variability. Variability in conventional clinical measures (within individuals, between clinical trial sites, and between different countries) erode signal detection and thus necessitate higher sample sizes to be able to detect therapeutic

[1] 83 Fed. Reg. 28851 (June 21, 2018).

effects. It would be beneficial if the final guidance provided advice to help ensure that study designs are rigorous while making the path to approval more efficient. Specifically, the updated guidance should encourage sponsors to implement promising new methodologies in development programs and show a clear regulatory pathway towards the acceptance of novel endpoints.

- Janssen disagrees with the categorical distinction between partial responders and non-responders (TRD) and the proposed requirement to study TRD in only monotherapy studies. Respectfully, we would like the Agency to consider an alternative approach, in which the study design and study populations are based on the pharmacological properties of the study drug and relevant clinical data.
- Recognizing recruitment challenges and high unmet need for safe and more effective treatments for pediatric and adolescent patients with major depression, Janssen requests the Agency to consider innovative approaches and flexibility in the required number of adequate and well-controlled short-term clinical studies in these patient populations.

Janssen appreciates the Agency's time and consideration in review of Janssen's comments. Janssen welcomes the opportunity to discuss these comments further and ask that you contact Jadwiga Martynowicz at 1-609-730-7028, or at the following email, jmartyn1@its.jnj.com.

Sincerely

Jadwiga Martynowicz, DM, MS
Senior Director, Global Regulatory Leader
Janssen Research & Development, LLC

Attachment

Attachment

Comments on FDA Draft Guidance: Major Depressive Disorder: Developing Drugs for Treatment

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM611259.pdf

GENERAL COMMENTS
The Draft Guidance, is written at a high level, emphasizing that sponsors should seek advice from the Agency early on study designs and statistical considerations. Clinical development in depression continues to suffer from high failure rates due to high placebo responses and intra-/inter-subject variability. Variability in conventional clinical measures (within individuals, between clinical trial sites, and between different countries) erode signal detection and thus necessitate higher sample sizes to be able to detect therapeutic effects. It would be beneficial if the final guidance provided advice to help ensure that study designs are rigorous while making the path to approval more efficient. Specifically, the updated guidance should encourage sponsors to implement promising new methodologies in development programs and show a clear regulatory pathway towards the acceptance of novel endpoints.
We disagree with the categorical distinction between partial responders and non-responders (TRD) and the proposed requirement to study TRD only in monotherapy studies. We would like the Agency to consider an alternative approach, in which the study design and study populations are based on the pharmacological properties of the study drug and relevant clinical data.
Recognizing recruitment challenges and high unmet need for safe and more effective treatments for pediatric and adolescent patients, the Agency is requested to consider innovative approaches and flexibility in the required number of adequate and well-controlled short-term clinical studies in these patient populations.

SPECIFIC COMMENTS ON TEXT

Line Numbers	Comment and Rationale	Proposed change (if applicable)
55-57	The guidance states the focus is on MDD and some principles may be applicable to clinical trials of drugs intended to treat other forms of depression. Could the Agency clarify what is meant by other forms of depression?	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 **(i.e., …).**

	It might be worth clarifying whether the intent of this guidance includes MDD with anxious distress.	
77-78	Given this statement, it might be useful to organize information presented in the guidance according to "traditional" drugs and "rapid-acting" drugs.	Consider organizing information contained in the guidance into separate sections: (1) “traditional” and (2) “rapid-acting” drugs to make clear distinctions in requirements.
77-79	Please consider making statements in this section consistent with text provided in lines 151-152.	Please amend the following sentence to include the bold text: 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 **8** weeks to show their effect.
92	The guidance indicates that Olney lesions have been observed with the class of drugs, N-methyl-d-aspartate (NMDA) receptor antagonists. However, this may not occur with all NMDA compounds, therefore, we suggest providing a qualifier when speaking about these compounds.	For example, **some** N-methyl-d-aspartate (NMDA) have been found to cause Olney lesions…
111-113	It would be helpful if the guidance provided more details about “specific studies and methods of analysis” particularly for “traditional” and “rapid-acting” antidepressants.	Please consider providing additional details on specific study designs and methods of analysis into the guidance related to “traditional” and “rapid-acting” antidepressants.
115-117	This seems specific to drugs that have known ligands or biomarkers.	Please consider including clarification provided in bold text: For all antidepressants, sponsors should conduct pharmacodynamic studies, such as in vivo receptor binding studies or biomarker studies **(when ligand and/or biomarkers are known)**, to initially identify appropriate dosage ranges, and these should be followed by clinical endpoint dose-response studies.
117-121	Regarding the statement “sponsors generally should include at least 1 dose-finding trial using a fixed-dose design with at least 3 fixed doses”:	Please consider amending the guidance in line 117-121 to make it less prescriptive and to indicate that the number of doses

	This seems like a strong (and specific) recommendation. With newly developed statistical methods like Multiple Comparison Procedure – Modelling (MCP-Mod), this may not be necessary. In addition, there are compounds where multiple doses may not be considered due to safety concerns. Thus, the number of doses tested in a dose finding study should be determined on a case-by-case basis and justified by the sponsor.	tested in a dose finding study should be determined on a case-by-case basis and justified by the sponsor.
123-124	An option should be for the sponsor to assess a molecule's overall potential to interact with other medications. If this potential interaction is minimal, then studies of the antidepressant with concomitant medication may not be needed.	Please consider including the following text to clarify need for drug interaction studies: "To develop an antidepressant intended for adjunctive therapy, early assessment of pharmacokinetic interaction with the background therapy is highly recommended." **Specific studies may not be needed if the antidepressant's overall potential for drug-drug interactions, particularly impact on the CYP450 system, is demonstrated to be low. Physiologically based pharmacokinetic (PB/PK) modeling may be used to inform the strategy**.
144-145	This sentence ("A substantially earlier or larger effect could be demonstrated in an active control superiority trial") is unclear. Is the Agency saying that a comparison to another treatment could be done by showing a large effect size compared to placebo if the comparison treatment is included as a separate arm in a placebo-controlled study? Please clarify.	Please consider providing clarification related to effect size in an active control superiority trial.
161-164	Fluctuations in symptoms in subjects with MDD over time is common. Would suggest to not set too conservative a bar in requiring response/remission maintained at every timepoint.	Please consider including clarification provided in bold text below: "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. **However, it is recognized that patients with depression could have occasional, transient mood fluctuations even following a response or remission to a new treatment. Thus, a small number of excursions or deviations should be allowed.**
161-164	Above 6-8 weeks is mentioned. For a rapid-acting antidepressant, if intended for repeated use, is the 6-8 weeks duration also appropriate (e.g., 4 to 6 weeks)? In addition, are p-values on timepoints other than the primary early timepoint acceptable? Could statistical significance also then be acceptable to indicate in a graph of means over time for the label?	Please consider providing further clarification on showing drug placebo differences over time.
204-217	FDA acknowledges in the current guidance, two treatment populations, partial responders to antidepressants and non-responders, patients with treatment-resistant depression (TRD). However, the guidance does not suggest how treatment failure is determined in these two populations. Furthermore, the draft guidance does not indicate whether clinical history and medication records can be used to document treatment failure or whether prospectively documenting treatment failure is required. Identification of patients for enrollment into clinical studies to support a separate indication of TRD may also be done by capturing historical data on prior response using validated measures (e.g. ATHF, MGH-ATRQ) and current symptom severity (Iovenio and Papakostas (2012).	Please consider adding into this section acceptable means for assessing treatment failure, including use of clinical history and medical records to document failure.
214-216	TRD is not well defined which is acknowledged by the Agency. TRD seems to be defined as a failure to respond to 2 or more treatments (consistent with Symbyax label). Please clarify in the final guidance what the Agency means by "not responded"	Please provide clarification on these points in the final guidance.

	(e.g., no improvement, small amount of improvement, <50% improvement).	
	Indeed, the difference between partial responders and non-responders is arbitrary and publications have shown similar degree of improvement between the two patient groups with adjunctive therapy (Nelson et al 2011, and/or 2012, EFPIA White Paper 2014, Papakostas 2016). An indication for TRD shouldn't necessarily be for a monotherapy treatment. A new treatment for TRD will most likely be used as an adjunctive to antidepressant treatment. Consequently, the guidance should allow for a study design similar to add-on for TRD rather than requiring a monotherapy study. The proposed monotherapy study design for TRD is problematic as it inherently leads to differences at baseline between the 2 arms, when the oral antidepressant is discontinued in one arm and continued in the other. With such a design, the comparator group remains active, is enriched for tolerability, and baseline depression scores will likely differ as in the new drug arm only, the previous antidepressant is discontinued. This will lead to unreliable study result and a very high hurdle for any medication for TRD. Additionally, although the FDA does not specify the need for a prospective treatment failure in a study of TRD, operationally it would be difficult to blind the treatment to which the patients have failed using an all comers design.	The final guidance should allow for an adjunctive study design for the TRD patient population where the comparison is to placebo rather than requiring a monotherapy study with the previous oral antidepressant as the active comparator.
251-252	For secondary endpoints, it would be valuable for the Agency to provide advice related to accepted patient/self-reported outcomes measures, in addition to the clinician rated outcomes.	Recommend that the final guidance provide general guidance on patient-reported outcomes measures that may be accepted as secondary study endpoints.

269-271	It is likely that sponsors would have seen blinded data. Thus, it would be useful to clarify this sentence by adding "unblinded" efficacy data…	Please consider amending the following sentence to include “unblinded”: 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 **unblinded** efficacy data in hand.
299-304	FDA guidance indicates extrapolation of adult efficacy data to support efficacy in pediatric MDD is not possible and that two independent adequate and well-controlled clinical trials short-term study in pediatric patients, in addition to pharmacokinetic and safety information in the relevant pediatric age groups are required for a pediatric claim. Recognizing recruitment challenges and high unmet need for safe and more effective treatments for pediatric and adolescent patients, the Agency is requested to consider innovative approaches and flexibility in the required number of adequate and well-controlled short-term clinical studies in these patient populations.	Agency is requested to consider innovative approaches and flexibility in the required number of adequate and well-controlled short-term clinical studies in these patient populations.