Depression and Bipolar
Support Alliance

August 20, 2018

Commissioner Scott Gottlieb
U.S. Department of Health and Human Services
Food and Drug Administration

RE: Major Depressive Disorder: Developing Drugs For Treatment; Guidance for Industry
Docket # 83 FR 28851
Depression and Bipolar Support Alliance Comments

The Depression and Bipolar Support Alliance (DBSA) appreciates the opportunity to comment on FDA's draft guidance for industry related to developing drugs for treatment of major depressive disorder. We comment from the perspective of DBSA's principle constituents, the almost 16 million people living with MDD. On behalf of these under-voiced stakeholders, we welcome this update on *Guidelines for the Clinical Evaluation of Antidepressant Drugs* issued in 1977.

The mental health community feels abandoned as the number of pharmaceutical companies willing to invest in mood disorder research shrinks—by some accounts as much as 70% in the last decade. Yet, according to the Centers for Disease Control and Prevention suicides are the tenth leading cause of death in the United States accounting for 44,000 deaths a year. We note the potential positive impact clear regulatory guidance can have in facilitating research and investment that can save lives.

DBSA hopes that guidance will advance the stated mission of the 21st Century Cures Act: "to help modernize and personalize health care, encourage greater innovation, support research, and streamline the system." We believe all stakeholders share the goal of fostering innovative therapies that provide people with serious health concerns and their loved ones the ability to lead the lives they want and deserve.

We applaud the agency's efforts to improve the process for developing new treatments and assuring the safety of patients. It is in that spirit that we respectfully offer comment.

Background

Although the necessity of defining indications for regulatory purposes may constrain this guidance to addressing MDD only as defined by a fixed number of DSM criteria, we are not aware of any data distinguishing illness on specific DSM cutoff points. Many of our participants experience suffering and disability that does not conform to DSM defined major depression. Could drug development programs examine alternative nosology or simply show results specifically for strata defined by different levels of severity?

The draft guidance divides pharmacological intervention into two phases: short-term (i.e., treatment of a depressive episode) and maintenance (i.e. relapse prevention).

Yet, only 25.6% of respondents to DBSA's 2016 "Depression Experiences and Treatment" survey indicated that their depression treatment was completely effective. Those whose depression is

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ameliorated by antidepressants often experience only partial remission and/or multiple, often worsening relapses.

For the majority, the questions are less about acute vs maintenance than non-response, partial response, or loss of response to a prior (approved treatment). Can clinical trials report the conditional probability that a person will respond to a new drug based on their response to a prior medication? Could a patient centric guidance provide recommendations on how to collect prior treatment response and report those outcomes?

Addressing the Unmet Need

The efficacy of MDD clinical trials declined from 55% in 1983-1994 to 50% in the time period 1995-2008.[1] Among the reasons often cited for low success rates in clinical trials is high placebo response[2]. This issue becomes a particular challenge in MDD trials where the lack of biomarkers must often give way to soft makers. Some alternative solutions such as the placebo lead-in design have shown promise, but have proven costly and effective in solving this challenge.[3] We favor reasonable strategies for mitigating high placebo response.

We enthusiastically support Commissioner Gottlieb's July 25, 2018 testimony, "As part of the FDA's broader innovation, we are encouraging the use of state-of-the-art innovations such as adaptive trials, modeling, and simulations to allow an evaluation of a product's safety and effectiveness."

We encourage the FDA to provide guidance that balances support for new models and innovation with rigorous demonstration of safety and consideration for potential confounds such as functional unblinding.[4] New models should reduce the life and death health risks of patient-subjects being exposed to investigational products and placebos, as well as speed approval.

Recognizing Whole Health Implications

We agree with the FDA that: "Geriatric patients and patients with renal insufficiency, cardiac disease, chronic pain and hepatic impairment should be included in trials during drug development, if feasible." Choosing between effective treatment for a comorbidity and mental health is counter-productive: individuals living with mental health conditions on average die 25 years sooner, not as a result of suicide, but as a result of myriad co-occurring conditions that can be exacerbated by and/or exacerbate MDD. Treating both MDD and any co-occurring conditions—recognizing and allowing for their complex relationships—is imperative to achieving optimal results.

Since trials are seldom acutely powered to show statistically significant results for these important subgroups, we would like to see results comparing the effects for these important groups reported in MDD clinical trials.

Conversely, depression co-occurs with many common general medical conditions, but we have little insight into the benefit treating depression might have on the course and outcome of chronic life shortening medical conditions. Could the FDA encourage collecting basic medical outcome measures from those patients entering MDD trials with common chronic conditions such as hypertension, diabetes, COPD, liver disease, or cancer?

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We are encouraged that Commissioner Gottlieb in his July 25, 2018 testimony recognized the need to work with patient communities "to elevate patient voices in developing new medical products to treat their diseases."

We encourage the agency to help amplify the patient voice and provide guidance that informs the development and evaluation of new products around patient-centered outcomes—outcomes that contribute to the whole well-being of patients given their heterogenous life circumstances and wellness issues.

DBSA appreciates the positive relationship we have built with the FDA—primarily with the Center for Drug Evaluation and Research, Division of Psychiatry Products. We look forward to sharing the patient perspective at the upcoming DBSA externally-led Patient Focused Drug Development Meeting on November 16, 2018. At that meeting we will be sharing results from the Supporting Wellness survey that commenced on August 1, 2018. Initial responses to the open-ended question: *What Does Wellness Mean to You* fall into several categories:

- Health in body, mind, and soul
- Living a quality life
- Ability to function (work, relationships, community)
- Lack of fear and insecurity
- Feeling normal
- Having a full meaningful life

Efficacy Endpoints

DBSA understands the pragmatic need for clinical outcome endpoints. We appreciate the November 27, 2017 guidance that the Qualification of Symptoms of Major Depressive Disorder Scale, a Patient-Reported Outcome Instrument for Measurement of Symptoms of Major Depressive Disorder, is qualified for exploratory use to measure symptoms.

Rather than viewing "clinician-rated outcome measures in competition with patient reported outcomes, we see them as complementary. While clinician reported outcome measures may be viewed as more sensitive to change than patient reported outcome measures, we believe every trial should require a PRO efficacy measure. We do not understand the rationale for counting a patient as a responder who perceives no subjective benefit. Hence, it would be of particular interest to see results for RCT subjects in which these different perspectives are discordant versus concordant and have sponsors explain these results.

DBSA participants and their families recognize MDD as a chronic condition and need information on durability of response. Acute outcomes and relapse following randomized discontinuation are not as useful as knowing the likelihood of social and occupational recovery. We suggest reporting outcomes for response sustained over meaningful periods of time such as 6-12 months rather than at week 6 or week 12 on legacy measures and adding at least one patient centric life satisfaction measure to all MDD clinical trials.

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DBSA also appreciates the acknowledgement that secondary endpoints that "assess other domains of symptom improvement" can be relevant for labeling. Moreover, we are encouraged that the FDA approved elements from the patient reported outcomes scale SGRQ, which is used to measure outcomes for patients living with Chronic Obstructive Pulmonary Disease (CPOD) for post marketing. In support of that effort, DBSA looks forward to sharing results from the Supporting Wellness survey at the externally-led patient focused drug development meeting. This survey provides respondents the opportunity to identify and rank dimensions of wellness beyond the Clinical Global Impression (CGI) and the Sheehan Scale.

Among the topics explored in the survey are dimensions of wellness not currently captured by any of the FDA approved or under consideration primary and secondary endpoint tools. We ask that this valuable patient input be considered for inclusion prior to any final Major Depressive Disorder: Developing Drugs For Treatment; Guidance for Industry is issued.

Conclusion

DBSA acknowledges the constructive intentions and hard work that went into developing the Major Depressive Disorder: Developing Drugs For Treatment; Guidance for Industry. This is the first guidance in almost forty years and much has changed in the research, technology and science associated with MDD. We sincerely hope that the agency will accept our offer of assistance and technical expertise as the guidance development process moves ahead. As DBSA seeks to promote the development of better treatment options, both pharmacologic and non-pharmacologic, we want to work with FDA to explore the steps that need to be taken in order to break out from the current dynamic of incremental, slow improvement to one of exciting breakthroughs. Part of this transformation requires changing the way we measure success, and we urge the FDA to look for guidance from those living with mental health conditions to bend the focus of scientific discovery towards the things that matter most to us.

Sincerely,

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Citations

[1] Ni A. Khin, MD; Yeh-Fong Chen PhD; Yang Yang, PhD; Peiling Yang, PhD; Peiling Yang, PhD; and Thomas P. Laughren, MD. *Exploratory Analyses of Efficacy Data From Major Depressive Disorder Trials Submitted to the US Food and Drug Administration in Support of New Drug Applications.*

[2]Juan Undurraga and Ross J Baldessarini Department of Harvard Medical School, Psychopharmacology Program and International Consortium for Psychotic and Mood Disorders Research, Malman Research Center, McLean Division of Massachusetts General Hospital, Boston, MA, USA. Bipolar Disorders Program, Department of Psychiatry, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain. *Randomized, Placebo-Controlled Trials of Antidepressants for Acute Major Depression: Thirty-Year Meta-Analytic Review.*

[3]Lee Baer & Anastasia Ivanova, Department of Psychiatry, Massachusetts General Hospital & Harvard Medical school, Boston Ma, USA. Department of Biostatistics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. *When should the sequential parallel comparison design be used in clinical trials?*

[4]Maurizio Fava, A. Eden Evins, David J. Dorer, David Schoenfeld, Department of Psychiatry and Biostatistics Center, Massachusetts General Hospital and Harvard Medical School, Boston, Mass., USA. *The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies and a Novel Study Design Approach.*

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