3 July 2019

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2019-D-0849

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment regarding the guidance document: *Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry*

The ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprised of scientists, clinicians, trialists, statisticians and drug developers from both industry and academia, received compensation for comments provided. Comments represent personal opinions and not that of the institution, agency, or company affiliation of group members.

The ISCTM formed a group, led by Manisha Madhoo and James Rawls to review and provide comments on behalf of the Society. The authors (in alphabetical order) of the comments provided below are:

Lawrence Adler, MD, *Clinical Insights, Inc*
Evdokia Anagnostou, MD, *Holland Bloorview Kids Rehabilitation Hospital, University of Toronto*
Stacey Boyer, PhD, *Cerevel*
Phillip Chappell, MD, MBA, *Pfizer Inc*
Denis Curtin, PhD, *Signant Health*
Gary Kay, PhD, *Cognitive Research Corporation*
Michael Klein, PhD, *Controlled Substance Scientific Solutions LLC*
Manisha Madhoo, MD, *Takeda (co-chair)*
Atul R. Mahableshwarkar, MD, *Revance Therapeutics*
Hilda Maibach, MS, *Indigo RDD*
Gahan Pandina, PhD, *Janssen Pharmaceutica Inc*
James Rawls, PharmD, *Sunovion Pharmaceuticals Inc (co-chair)*
Colin Sauder, PhD, *Adams Clinical*
Joyce Tsai, PhD, *Sunovion Pharmaceuticals Inc*
Silvia Zaragoza-Domingo, PhD, *Neuropsynchro*

**COMMENTS ON THE ATTENTION DEFICIT HYPERACTIVITY DISORDER: DEVELOPING STIMULANT DRUGS FOR TREATMENT GUIDANCE FOR INDUSTRY:**

**General Comments**

ISCTM welcomes this guidance and is encouraged that the FDA has provided detailed recommendations to sponsors developing stimulant drugs for treatment of attention deficit hyperactivity disorder (ADHD). Although stimulants are considered first-line treatment medication for ADHD there remain limitations

and risks related to their utilization as noted in the guidance document (Lines 126-130). Therefore, to spur the development of novel drugs for the treatment of ADHD we encourage FDA to provide complimentary guidance in the near future regarding non-stimulant drugs developed for the treatment of ADHD in pediatric and/or adult patients.
The ISCTM looks forward to the ultimate adoption of guidance that clearly advances the methodology and efficiency of drugs intended to treat patients with ADHD and would readily participate in further public debate to achieve this goal.

**I. Introduction and Background**
The document states in lines 19-20 that *"this guidance does not address development programs for nonstimulant drugs."* Further in the document (lines 36-40) it is stated that *"the principles outlined below apply to drug development programs for methylphenidate and amphetamine products developed and submitted under the 505(b)(2) application pathway…as well as for novel (i.e., new molecular entity (NME)) stimulant drugs."*
It is not clear why the principles outlined in the guidance document would be different for non-stimulant NMEs. The ISCTM appreciates the guidance that is provided for short-acting stimulant drugs but considering the abundance of approved products within that category, it would be important to note in the guidance document where applicable the recommendations would diverge for non-stimulant NMEs. This would encourage and facilitate the development of newer agents.

**II. General Considerations**
Throughout the guidance document (e.g. lines 25-26) there is a reference to stimulant drugs. While examples of stimulant drugs (i.e., methylphenidate and amphetamine) are provided it would be important for this guidance document to provide a clear definition regarding for a "stimulant" drug. In the absence of such guidance, the reader may assume that "stimulant" drugs are those with either the same receptor binding profile or purported mechanism of action[1] as methylphenidate or amphetamine.

**IIA. Clinical Pharmacology**
- Lines 72-75 provide guidance regarding the number of studies required to support approval in pediatric and adult patients where it is stated that *"In general, the pathophysiology, disease characteristics, and treatment outcomes in ADHD are sufficiently similar between pediatric and adult patients such that, with two positive pediatric studies, an adult indication can be supported by a single trial in adult patients*." The ISTCM agrees with this guidance, but clarity should be provided when the treatment outcomes for the investigation agent differ across the patient populations. For instance, would this guidance still be applicable if the clinical study in adults demonstrate that the investigational agent is effective with a favorable benefit/risk profile, but the investigational agent is not effective or the benefits do not outweigh the risks in children? The ISCTM submits that FDA should approve products for adults only in the absence of an indication in children or adolescents if a new drug application contains adequate information to assess the effectiveness and safety of the investigational drug across the patient populations, which would allow an assessment of the benefit/risk profile across each of those populations.

**IIB. Trial Design**
- The ISCTM agrees with the patient age groups noted in lines 77-82, *"…. The relevant pediatric age groups are 4 to 5 years of age, 6 to 12 years of age, and 13 to 17 years of age."* The guidance document further notes that a new drug application at the time of original submission should contain *"….one study in adolescent patients (13 to 17 years of age) and one study in younger pediatric patients (4 to 12 years of age) to provide substantial evidence of effectiveness…."*. The ISCTM is concerned that the pediatric patient age group is too broad and should be limited to 6-12 years of age at the time of submission of the original New Drug Application. Studies in patients 4-5 years of age should be a post-marketing commitment based in part on the following:

[1] Package Insert:

- Including children 4-5 years old in a clinical study creates methodological issues as it is the experience of ISCTM members that it is difficult to effectively utilize efficacy assessments (e.g., SKAMP) in these younger patients. This would compromise signal detection in these younger patients and potential the outcomes of clinical study.
- In the experience of ISCTM members, younger children, in particular 4-5 years old are very difficult to recruit. This would result in very few, if any, 4-5 years old being included in the clinical study. Also, it is not clear if a minimum number of 4-5 years old would be required to be included in the clinical study to obtain approval for the entire age range (4-12 years old).

- Lines 111-113 state that *"Patients should be randomized to drug or placebo, without open-label titration or dose-optimization before randomization that may obscure important safety findings."* It is not clear why dose-optimization with open-label titration would *"obscure"* safety as such a design would provide important safety information and guidance regarding safety and dose titration. Thus, clarity is needed regarding this particular point and the rationale to support the recommendation. It would also be important to clarify if this recommendation is related to a short-term efficacy and safety study, as open-label titration and dose-optimization have been considered standard and acceptable design elements for long-term (maintenance) efficacy and safety studies.

- ISCTM agrees with the acceptable primary efficacy measure suggested in the guidance document (lines 115-124). We would, however, like to encourage FDA to consider and note within the guidance document that a cognitive endpoint could be considered as a co-primary. FDA should also consider diary data and quality of life as a means of assessment.

- Occurrence of early morning return of ADHD symptoms and behaviors in subjects treated with short-acting stimulants has been extensively reported in the literature[2,3,4,5,6,7,8]. In studies utilizing a simulated classroom design, it would be important for FDA to comment within the guidance document on how they will consider and interpret such a finding especially for long-acting (>12 hour) stimulant or non-stimulant New Molecular Entities.

- ISCTM agrees with the list of adverse events of special interest in lines 126-130. However, further clarity, with specific questionnaires cited, regarding how FDA expects the assessment of sleep, appetite, mood and psychotic symptoms to occur within a clinical study would be helpful. This is particularly important for younger patients (<12 years old) as ISCTM is not aware of any validated tools available to assess psychotic symptoms in this patient population. It should also be noted in the guidance document how FDA would consider data from an adverse event questionnaire juxtaposition spontaneous reports regarding the same adverse event.

**IIC. Pregnancy**

- The first sentence in this section (Line 134) appears to encourage Sponsors to include women of *"reproductive potential"* in a clinical study since they are sometimes prescribed ADHD medications. However, the following sentence (Line 135) pivots to *"pregnant women"* and encourages Sponsors to include such women in a clinical study. ISCTM recommends clarifying this text to clearly indicate if women of reproductive potential and/or pregnant women should be included in a clinical study. ISCTM supports the former but not the latter and recommends that Lines 135-137 be replaced with the following text:

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[2] Brams et al., 2012
[3] Childress et al., 2015
[4] Childress et al., 2018
[5] Swanson et al., 2004
[6] Wigal et al., 2010
[7] Wigal et al., 2013
[8] Wigal et al., 2017

*"Women of reproductive potential should be enrolled in a study only if the potential benefit justifies the potential risk to the developing fetus."*

- Also, the section title should be changed to "Women of Reproductive Potential"

**III. Methylphenidate AND Amphetamine 505(b)(2) Development Programs**

- The comments provided regarding Section IIB (Trial Design) related to the conduct of clinical studies in children 4-5 years old are applicable to the recommendations in Lines 208-211 of this section.

**IV. New Molecular Entity**

- Instead of instructing Sponsors to conduct a human abuse potential study, the guidance document should state that the study should be conducted in accordance with *FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (2017)*