14 March 2016

To: Department of Health and Human Services, Food and Drug Administration

Re: Docket # FDA–2015–N–5106

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment: Clinical Outcome Assessment Compendium.

The International Society for CNS Clinical Trials and Methodology (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 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 Adam Butler, to review and provide comments on behalf of the Society. Authors (in alphabetical order):

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COMMENTS ON THE CLINICAL OUTCOME ASSESSMENT COMPENDIUM:

General Comments

ISCTM is dedicated to improvements in CNS outcomes and as such focused on the sections relevant to this area. In general, we find the efforts of the Drug Development Tool Qualification Process and the Clinical Compendium to be refreshing, proactive initiatives on the part of the FDA to address significant gaps between industry and regulators. However, there are a number of areas that would benefit from greater clarification or exploration. In general, the target audience and the key stakeholders in the Compendium's development should be more clearly defined.

ISCTM is concerned that this guideline may create an incentive for drug developers to continue to implement trial designs that are predicated on current possibly outmoded methodologies and limit innovation and the development of improved measurements. This concern comes from our observation that the Compendium is focused on establishing current practice based on past precedent. There are disclaimers that the mentioned measures should not necessarily be the primary measures and the compendium recommends that sponsors discuss specifics with the respective review division. However, the selection criterion that includes measures based on registered drugs leads to a bias reinforcing the use of older scales and measures, and may impact the introduction of newer and more suitable instruments.

Comments Regarding Alzheimer's Disease and Dementias

Alzheimer's and dementia is a hugely important area. Great focus has been placed on stimulating new research and development of new cures in the spectrum of Alzheimer's disease and other dementias. This includes mild-to-moderate AD, prodromal AD, mild cognitive impairment, and in unique disease-modification AD trials. Despite extensive regulatory involvement and consultation in the design and implementation of numerous trials covering these areas, they are not covered in the current Compendium. Outcome measures such as the ADAS-Cog, the Clinical Dementia Rating, and the geriatric Depression Scale are all used widely, with clear FDA input, in numerous industry trials and they should be included here?

In addition, programs addressing the neuropsychiatric symptoms of Alzheimer's disease and Parkinson's disease have both received unique FDA scrutiny and review in recent years. Up to 80% of patients with dementia experience neuropsychiatric symptoms including depression, apathy, agitation, aggression and sundowning during the course of their dementia. There are currently no approved treatments for these symptoms. In some cases, the FDA has been deliberate giving examples regarding COA selection for these populations, but those recommendations are not captured in the Compendium.

For MCI the document mentions "Currently unnamed (performance outcome tool to assess instrumental activities of daily living (IADLs)." Is there any more specific guidance on what this tool or measure should look like from the FDA's point of view, or is any reasonably validated performance based measure of IADLs sufficient?

Comments Regarding the Cognition in Schizophrenia and the MATRICS Consensus Cognitive Battery

The FDA has previously identified cognition in schizophrenia as a reasonable clinical target. The MATRICS Consensus Cognitive Battery (MCCB) is an instrument developed during a consensus-building process that included representatives from academia, industry, and the FDA. Although it was developed prior to the COA DDT guidance, and no treatments have yet been approved for this difficult area, we suggest that it should be added to the Compendium.

Comments Regarding Abuse Liability Outcomes

For CNS active compounds, assessing the potential of Abuse Liability is a requirement, especially in Phase 3 trials. There are numerous COAs already endorsed or approved for use in these situations, they should be represented here. These are some of the validated instruments that the Controlled Substances Staff (FDA) has presented as outcomes of interest for these trials.

Opiate withdrawal scales:
Clinical Opiate Withdrawal Scale (COWS)
Subjective Opioid Withdrawal Scale (SOWS)
Benzodiazepines withdrawal scales:
Physicians Withdrawal Checklist PWC-20 and PWC-34
Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)
Clinical Institute Assessment of Withdrawal Benzodiazepines (CIAW-B)
Ashton Rating Scale
Stimulants withdrawal scales:
Amphetamine Withdrawal Questionnaire (AWQ)
Cocaine Selective Severity Assessment (CSSA)
Cannabinoids withdrawal scale:
Cannabis Withdrawal Scale
SSRI withdrawal scale:
Discontinuation Emergent Signs and Symptoms Checklist (DESS)

Comments Regarding Other Disease Areas and COA

There are some examples of diseases or disorders that have seen limited development focus, or limited drug approvals, in recent years. These all have historical, well-established COA measures but should be given further consideration for inclusion. This exemplar list isn't conclusive, but examples include:

- Liebowitz Social Anxiety Scale (LSAS)
- Yale-Brown Obsessive Compulsive Scale (Y-BOCS)
- Hamilton Anxiety Scale (HAM-A)
- Sheehan Disability Scale
- Extrapyramidal Symptoms Rating Scale

General Comments Regarding the Compendium and the Process

The FDA has asked drug developers to pay special attention to pediatric and other special populations during the planning and execution of their programs. The current Compendium includes only a small number of COAs specific or limited to pediatric patients. As age is one of important factors in assessment, we would like to ask FDA to capture COAs for "child", "adolescent", "adult", and "geriatric" for each disease, if applicable.

Domains are increasingly being utilized in drug development programs, domains that cross traditional diagnostic categories as targets for treatment interventions such as anhedonia, impulsivity, aggression, agitation, suicidality, motivational deficits etc. – all of which may represent unmet needs and could offer possibilities for development of targeted and personalized treatments. The Compendium in the current form could limit this approach, and our suggestion would be to allow inclusion of measures relative to their symptom measurement targets.

If the intention is to also include COAs that have not been approved specifically via the DDTA process, but are familiar to the FDA either as gold-standard measures, or measures routinely used in disease-

specific trials, then a comprehensive list of those measures could be included. Conversely, if a gold-standard COA or a routinely used COA, known to industry, does not appear in the compendium, an open disclosure of why the measure was excluded will be important for the compendium to become a valuable resource for FDA approved/preferred COAs and their utilities and applications.

There are numerous disease areas that present a tremendous unmet need, and have seen no treatments approved in recent years. But limiting the introduction of new COAs to only those that have completed the COA DDT Qualification presents a significant burden to drug developers to take on these new areas, if the compendium is presented in a manner that will incite drug developers to adhere to it from perceiving it as the preferred list of COAs that will expedite FDA reviews of trial data. Novel outcome development and validation programs are expensive and time-consuming, and the criteria for how a Clinician-Reported Outcome will be evaluated in this framework are not clear. Allowing an alternative for new or novel outcomes to be introduced may be useful in encouraging drug developers to take on these difficult areas and eventually benefit patients.

Patient-Reported Outcomes and Health Economics measures are an increasingly important area of focus in clinical research. Yet in the psychiatry section there is only one indication for which a patient-reported outcome measure is mentioned. This is a gap that should be addressed.

The Compendium would benefit from specifying situations where electronic modalities were available for specific COA.

There are no guidelines or instructions on how sponsors should utilize the COA Compendium. It would be helpful to provide the end user with guidance on when the Compendium should be consulted and when alternatives should be considered.

For outcome assessments that have not been qualified, the “Not applicable” is somewhat misleading and does not provide sufficient information to the end user. A better phrase might be “Not qualified” or “Did not follow qualification process” or similar wording to better indicate the status.

Technical Comments Regarding the Compendium

It would be helpful to make the document a standalone table, i.e., to include the objectives for developing the Compendium which are listed on the website, and to provide more details about the selection process rather than referring people to another website, as part of the Compendium itself.

It may be helpful to include a column to show where the entry in the compendium originated from i.e. drug approval 2003-2013, FDA COA qualification program, primary/co-primary in ongoing trial etc. This will be particularly useful when this program expands beyond COA DDT Qualification.

To avoid error in judgment during selection, bibliographic references are important for obtaining more information on the psychometric properties and performance of COAs in the settings, geographic regions and demographics, and also relevant published meta-analyses. COA type generally denotes utility (i.e. screener, diagnostic, functional/treatment monitoring), and could be presented in a distinctive manner to be meaningful in the COA selection process, i.e. specifying type also as a PRO, ClinRO, ObsRO, combined types, etc.

In the current Compendium, both COA name and COA type are included in the same field. Distinguishing these fields could be helpful in both organizing and searching the Compendium. In addition, many COAs have versions or version information that may be specific to their use or current validity. The Compendium should track version numbers where relevant.

A multitude of new COAs are developed every year, while tens of thousands of measures already exist, in multiple versions some of which have been vetted by their developers, while others have no source of reference for reason and validity of modifications. As the FDA compendium project evolves, it will be necessary to maintain its content on a regular basis, and to distinguish among validated and unvalidated modifications of the same measure.

From this document is not clear how often the COA Compendium would be updated, eg, will be it updated immediately after a label using a new measure is approved? It would be helpful to provide to the end user an idea of how frequently the Compendium will be updated.

What was the rationale for establishing 2003 as the cut-off for the start date for the review of labeling? Many useful assessments may have been omitted that were used prior to 2003.