30 July 2010

Submission of comments on EMA Concept Paper on the Need for Revision of the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia

Comments from:

Name of organisation or individual:
International Society for CNS Clinical Trials and Methodology (ISCTM) www.isctm.org Submitted by *EMA Response Working Group* Chair: Douglas Feltner, MD

1) General comments

	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The International Society for CNS Clinical Trials, ISCTM, welcomes the opportunity to comment on the above listed paper. The ISCTM was chartered in fall of 2004 as an international society charged with providing a commercial free forum where key stakeholders from academia, industry and regulatory branches can discuss/resolve challenges specific to the design and methodological issues in CNS clinical trials. Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance. Work Group members included: Chair: Douglas Feltner, MD Steven Ascher, PhD, Johnson and Johnson; Miranda Chakos, MD, State Univ of New York Downstate Med Ctr; Nathan Chen, MD, PhD, Pfizer, Inc; David Daniel, MD, United BioSource Corporation; Nicholas DeMartinis, MD, Pfizer, Inc; Andrew C. Leon, PhD, Weill Cornell Medical College; Tom Macek, PharmD, PhD, Takeda; Randall Marshall, MD, Sepracor; Mark Opler, PhD, The PANSS Institute; Anne-Marie Quinn, Johnson and Johnson; Jill Rasmussen, MD, psi-napse; Nina R. Schooler, PhD, State Univ of New York; Jane Tiller, MBChB, FRCPsych, Cephalon Inc; Ibo Turkoz, Johnson and Johnson 1) The group unanimously agrees that the *Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia* should be revised. 2) The group found the level of detail in the 1998 guidance document too limited, leaving it subject to wide interpretation. We have listed a number of areas we would like to see addressed in depth, and in those areas where the Society has particular expertise, we have included more detail. We hope these comments are useful and look forward to the opportunity of responding to the actual guidance when it is released.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Sec3:Point2 Negative Symptoms		Below you will find a list of methodological issues in negative symptom trials we hope will be addressed in the guidance document. This list was generated by a group of representatives of academia and the pharmaceutical industry that met in a workshop format at the International Society for CNS Clinical Trials and Methodology (ISCTM) in September, 2009 in San Diego, California. This meeting elaborated on topics discussed at an earlier NIMH workshop chaired by Bryan Kirkpatrick in 2006 (1). 1. What are acceptable designs and duration for trials of agents that may be effective for both psychotic and negative symptoms? 2. What are the acceptable designs and duration for co-medications for negative symptoms that would added to an antipsychotic? 3. What are the characteristics of patients who are acceptable for negative symptom trials? 4. What are the desirable characteristics of measurement scales for negative symptoms trials and what rating scales are currently considered acceptable? 5. Is improvement of negative symptoms sufficient or is improvement on co-primary and/or global measures of function also required for regulatory approval? 1.Kirkpatrick, B.; Fenton, W.S.; Carpenter, W.T., Jr.; and Marder, S.R. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*, 32(2):214-9, 2006.	
Sec 3, Point 3 Placebo Use and Response		ISCTM supports the inclusion of a placebo group in trials intended to demonstrate the efficacy of schizophrenia drug candidates. Placebo controls are necessary to demonstrate and quantify efficacy in schizophrenia trials. The text of Section 2.1 (Use of Placebo) of the 1998 guidance requires updating to more clearly identify the trials in which placebo controls are needed to support specific efficacy claims. Further, the purposes (e.g. collecting safety data) for conducting trials that may lack placebo controls should be specified. If "suitable alternative designs" are thought to be appropriate for certain purposes, the designs and purposes should be specified.	
Sec 3, Point 4 Maintenance Therapy		As a chronic, recurrent illness, schizophrenia is characterized by irregular exacerbations of acute symptoms of the disease. The severity and character of these acute symptom exacerbations and the general course of the disease vary uniquely from patient to patient, but the general course is one of functional deterioration during the initial years of illness with plateauing of functioning at significantly lower levels than anticipated from premorbid expectations. Seldom do patients return to pre-diagnostic levels of function. Due to these individual differences, overall treatment needs vary both from patient to patient and within a single patient over the course of their illness. As such, the ISCTM supports the need for long-term efficacy and safety data for new treatments for schizophrenia. The current Guidance addresses the needs for long-term efficacy data, in that, Section 6.4.2 (Maintenance Therapy) includes direction to demonstrate that the "effect found in acute phase is maintained". The current Guidance appears to allow for randomized withdrawal (relapse prevention), double-blind extension, and separate double-blind non-inferiority trials, as well as other possible designs. While ISCTM believes that it is important to allow for alternative designs, ISCTM requests greater clarification or quantification of what constitutes "well documented efficacy in the maintenance treatment of schizophrenia". The Guidance should clarify more specifically which designs are acceptable to support a "maintenance" claim, and whether a particular design, such as a longer-term, double-blind non-inferiority trial with an active comparator, is preferred (provided the active comparator in these studies has previously demonstrated "well documented efficacy in the maintenance	

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treatment of schizophrenia.") Different study designs involving long-term treatment may address somewhat different scientific questions. Thus, the guidance should clarify which designs are more supportive of a "maintenance treatment" claim, and which might be more supportive of alternative labelling, such as, for example, "relapse prevention" or "long-term treatment effects".

ISCTM further suggests that issues of acute efficacy and safety be addressed separately from issues of maintenance of treatment effects. First, designs that attempt to establish both acute and longer term efficacy in the same study may leave clinically important questions incompletely addressed or unaddressed. In particular it is possible that optimal dose, dosing regimen, or other treatment or study population characteristics may differ for acute efficacy and maintenance treatment. Second, sample size may differ substantially between acute and maintenance studies, and this combined with duration of treatment issues may make such combined studies impractical to conduct. If time and cost requirements of a study are too onerous, valuable treatment agents may not be studied or the studies conducted may be poorly powered or improperly interpreted. Because of the complexity of designs that attempt to address multiple questions, it is suggested that issues of acute efficacy and safety be addressed separately from maintenance questions.

Finally, as written, the requirement for maintenance of effect within the Guidance is most relevant to an acute exacerbation of schizophrenia. The guidance does not, however, definitively define what would constitute evidence for maintenance of effect for negative symptoms or cognitive symptoms or timeframes for which maintenance of effect would be relevant for each of these symptom domains. To this end, ISCTM suggests that requirements for establishing maintenance of effect for these additional important symptom domains be clarified.

(Current maintenance guidance follows)

Due to the chronic character of schizophrenia (with relapses/recurrences), longer double-blind controlled studies are necessary to show that the effect found in the acute phase is maintained.

The usefulness of including more than one dose of the investigational product to investigate the optimal dose for long-term treatment should be considered.

Extension studies may be performed as long as they stay double-blind. A product with a well documented efficacy in the maintenance treatment of schizophrenia should be used as the active comparator. The duration of such a trial should be one year due to the natural course of the disorder and the assay sensitivity should be argued. Another possibility is a so-called relapse prevention study, in which responders to the acute treatment are included and randomised into a medication and a placebo group and for which rate of or time to relapse is used as criterion for efficacy. However, when this design is used, the duration of the acute therapy period probably needs to be longer than 6 weeks and it may be useful to stabilise the patients first during an open treatment period. A long-term placebo-controlled trial during 6 months also may be an option. If one of the latter two options is used, one needs to make sure that the protocol includes specific measures like close monitoring and the possibility to use rescue medication. Other designs also may be used, but the usefulness for the specific situation has to be shown or argued (see section 3.2).

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Sec3, Point 5 Combination Therapy		Antipsychotic combination therapy is common in clinical practice for treatment of residual symptoms of schizophrenia. With the ongoing development of antipsychotic medications that have novel mechanisms of action (such as glycine transporter inhibitors), there is an even greater need for the regulatory bodies to provide guidance with respect to clinical trial designs that would be appropriate to evaluate efficacy of adjunctive antipsychotic medications for treatment of residual symptoms of schizophrenia. Such guidance should address clinical trial designs that would best address the efficacy of the adjunctive treatment, including the need for a placebo adjunctive treatment as a comparator and the duration of trial required to establish efficacy of the adjunctive treatment. Guidance on the definition and duration of stability of residual symptoms and stability of primary antipsychotic treatment, as well as concomitant medications, during retrospective and prospective treatment period of the trials would be helpful. Other issues that could be addressed are the types of antipsychotic treatments that would be permitted as the primary antipsychotic in these trials, including whether both 1st and 2nd generation antipsychotics would be permitted and whether clozapine should be excluded. Recommendations on subject selection including the level of severity of residual positive symptoms that would merit treatment in these trials and exclusion of treatment resistant patients would also be helpful.	
Sec 3, Point 9 Cognitive Symptoms		ISCTM believes that cognitive impairment is an important and impairing symptomatic domain of schizophrenia. As such, guidance on all aspects of treatments for cognitive impairment associated with schizophrenia is needed. A separate guidance on treatments for cognitive impairment associated with schizophrenia should be considered. Specific issues that should be covered in the guidance are: • patient selection (stability of other symptoms, severity of cognitive deficits, minimizing potentially confounding medication side effects, primary diagnosis of study population Schizophrenia vs more broadly defined primary diagnoses), • acceptable primary outcome measures (cognitive batteries), secondary outcome measures, • study design (monotherapy trials for an agent thought to benefit both positive symptoms and cognition vs add-on designs for cognitive agents intended to be added-on to current antipsychotic treatments, acceptable study duration, need for placebo control); • whether a maintenance study (e.g. relapse prevention or 6 month parallel group) needs to be conducted in addition to shorter-term studies or whether shorter-term treatment studies are sufficient; whether short-term cognitive benefits would need to be shown to persist i longer term (e.g. 6 month) studies; • definition of a clinically meaningful benefit (Is showing improvement on a global or functional outcome needed in addition to showing improvement on a cognitive battery?) • whether pediatriac/adolescent and elderly studies will need to be conducted, and if so, what studies are needed, and which of these studies would need to be completed prior to marketing approval and which could be completed after marketing approval.	
Not included in Concept Paper Section 3 list		The ISCTM would respectfully draw attention to the committee to these additional topics. As above, in areas of our expertise we have included comment.	

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Functional Outcome Measures		Prevention, remission, and recovery for patients with schizophrenia and other psychotic disorders are important clinical and policy objectives.[i] Interventions that maintain low levels of psychopathology, and control symptoms over time, may permit patients to engage in productive social and occupational pursuits. Clinician and patient reported functional outcomes may also provide a unique insight to quality of life, compliance and overall patient care. In the interest of broadening the goal and scope of clinical development of new treatments, functional outcome measures may be useful for inclusion in clinical research studies. There are several well-validated measures, both general in nature (e.g. the GAF[ii]) as well as those that are specialized (e.g. the Personal and Social Performance Scale or PSP [iii] adaptations of the CGI[iv], and Subjective Wellness on Neuroleptics Scale[v]). In addition to the role of functioning in quality of life and as an important dimension of recovery, new targets for treatment, such as cognitive performance, appear to have important relationships to functional capacity. [vi] [i] Corrigan PW. Recovery from schizophrenia and the role of evidence-based psychosocial interventions. Expert Rev Neurother. 2006 Jul;6(7):993-1004. [ii] Startup M, Jackson MC, Bendix S. The concurrent validity of the Global Assessment of Functioning (GAF). Br J Clin Psychol. 2002 Nov;41(Pt 4):417-22 [iii] Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand. 2000 Apr;101(4):323-9. [iv] Haro JM, Kamath SA, Ochoa S, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand. 2003;107(s416):16-23 [v] Naber D, Moritz S, Lambert M, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr. Res. 2001;50(1-2):79-88. [vi] Leifker FR, Bowie CR, Harvey PD. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. Schizophr Res. 2009 Nov;115(1):82-7.	
Statistics		There have been a number of advancements in statistical methodology as applied to longitudinal clinical trials since the 1998 EMA schizophrenia guidance appeared. These advancements should be addressed in the updated schizophrenia guidance to indicate the types of statistical methods that might be utilized for specific types of trials at particular stages of drug development. One important area in which change has occurred is in the handling of missing data. A more or less universally acceptable method to handle missing data had been the concept of last observation carried forward (LOCF). This method was accepted and even required by health authorities as the primary tool for handling missing data in a longitudinal setting. While easy to implement, this method has a number of limitations, including over/under-estimating treatment effects (and the associated variance) and inconsistency with the course of the disease. More recently the FDA and other health authorities have in some circumstances allowed the use of methods such as mixed model repeated measures (MMRM) when faced with missing data, since MMRM methodology under the ignorable missing data framework provides a robust approach to estimating the true treatment difference and in controlling Type I error rates. Sensitivity analyses that evaluate missingness assumptions must be performed to assess the robustness of findings. All of the aforementioned analyses should be prespecified in the protocol. Since the statistical findings might be uninterpretable in the presence of high dropout rates, the dropout rates in a trial need to be considered when interpreting the efficacy findings. When	

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		analyzing time to event data (e.g., time to relapse in relapse prevention trials, particularly when different types of relapses may require separate analyses), methods such as proportion hazards regression (i.e., Cox regression) and log-rank testing are valuable tools. However, one needs to assess the assumptions about informative censoring.	
Implications of DSM-5		In the current request for comment it is clearly stated that revision of DSM-IV is a major factor in the need for revision of the NoG. DSM-5 will likely have an impact on the ways in which clinical trials are designed and conducted in schizophrenia even before DSM-5 is formally released in 2013. The ISCTM is well aware of these forthcoming changes. Our Autumn Conference (October 14) will include a session to examine the implications of the proposed DSM-5 classification for clinical trials in schizophrenia and other psychotic disorders. A member of the DSM-5 Psychosis Workgroup will present up-to-date information regarding diagnoses and how they are likely to change that will form the basis for discussion on the potential impact on conduct of future trials in schizophrenia. Commentary from representatives of EMA and FDA will complement the session. We believe that reviewing the discussion may be valuable to the group revising the NoG and will plan to submit a summary of the session following the meeting.	
Comparative Claims		It would be useful to consider addressing approaches for pursuit of comparative claims and labelling statements for efficacy and safety in the updated guidance. Substantial effort is being invested in efforts to demonstrate efficacy findings that differentiate compounds in development for schizophrenia from those that are currently available, in order to address areas of high unmet medical need. Some factors to consider include clinical trial design, clinical domains that may be pursued, and the level of evidence required for comparative claims or labelling statements. Factors to consider in clinical trial design include the selection of comparator, whether a placebo comparator would be required, and acute vs. long-term treatment study design approaches. Potential clinical domains to pursue include overall disease efficacy, positive symptoms, negative symptoms, cognitive deficits, functional outcomes, and remission. Guidance on the criteria for achieving comparative claims could advance efforts to develop treatments that address unmet medical needs as well, Outlining the degree of evidence required for different comparative claims would be helpful; it would be expected that a higher level of evidence would be required for a claim in the indication section of the product label than for efficacy information that would be listed in the clinical trial descriptions in the Pharmacodynamics section of the product label. Addressing these and other factors involved in pursuing comparative claims in drug development for schizophrenia in the updated guidance will support assessment of the efficacy and safety differentiation data that EMA will be receiving in future regulatory filings for drugs in development for schizophrenia.	
Assessing weight and metabolic effects of antipsychotics *		Guidance should be provided on assessing weight gain and metabolic effects associated with antipsychotic medications that might lead to diabetes, metabolic syndrome, or cardiovascular adverse events. Guidance is needed on which metabolic parameters to assess (e.g. lipids, glucose, Hba1c), how to assess drug effects on weight and metabolic parameters when the drug is used in combination with concurrent medications in combination trials, and whether comparative claims can be established for metabolic effects and weight gain. Guidance on the types of findings that suggest the need for additional evaluations, and guidance on what special safety studies might be done in these circumstances, would be helpful. In addition, it would be useful to clarify which schizophrenia sub-groupings (age, gender, chronic vs acute schizophrenia vs drug naieve) should be evaluated to determine whether they are more susceptible to adverse metabolic or weight effects. Finally, guidance could be provided on what behavioural and lifestyle variables (smoking,	

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		exercise, diet, etc) should be evaluated to determine whether they impact weight or metabolic effects associated with antipsychotic medications. Contextual information from clinical guidelines, the olanzapine label, and additional reference information is listed in the appendix below.	
Additional areas of interest		Group felt detailed guidance in the following areas would also be helpful: ➢ Efficacy issues o Guidance on claims for improving suicidal behavior and/or suicidal ideation in schizophrenia; ➢ Safety issues should be addressed in more detail: o Guidance on monitoring for and reporting on adverse events of suicidal ideation and behaviors. This is an area of active interest for ISCTM. A workshop addressing the methodological and technical challenges associated with suicidality assessment in clinical trials will be convened in October. ISCTM will be happy to provide outcome of that group's deliberation.	
*Appendix: Assessing weight and metabolic effects of antipsychotics		Appendix for Weight gain and Metabolic effects: ► Olanzapine Depot labelling • Lipid alterations ■ Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. ■ Patients treated with any antipsychotic agents, including ZYPADHERA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines ■ Recommendations for monitoring of patients for glucose, lipids, and weight. ■ Promote awareness of appropriate metabolic monitoring by distributing utilized published antipsychotic guidelines. Clinical Perspectives ► Nice Guideline 82 Schizophrenia Mar 2009 • Primary care and physical health ■ GPs and other primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year. Focus on cardiovascular disease risk assessment as described in 'Lipid modification' (NICE clinical guideline 67) but bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population. A copy of the results should be sent to the care coordinator and/or psychiatrist, and put in the secondary care note ► Metabolic and Lifestyle Issues and Severe Mental Illness – new connections to well-being; Expert Consensus Meeting Dublin April 2005 • Physical comorbidity in SMI ■ People with SMI are three times more likely to die prematurely from natural causes than people without mental health disorders. At least 50% of individuals with schizophrenia are thought to	

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		have a comorbid physical condition. ■ Impaired fasting glucose, platelet abnormalities and visceral fat deposition have been observed at higher rates in first-episode, drug-naive individuals with schizophrenia than in matched controls. Diabetes is two to four times more prevalent in people with schizophrenia and bipolar disorder. Cardiovascular disease (CVD) are the leading 'natural' cause of death in schizophrenia. ■ High-risk behaviours, such as smoking and drug abuse, an unhealthy diet and sedentary lifestyle, are also more prevalent in populations with SMI than in the general population – often as a result of social deprivation. Individuals with SMI are two to three times more likely to smoke and six times more likely to abuse drugs than the general population. ■ Schizophrenia appears to be associated with a range of both modifiable and non-modifiable cardiovascular risk factors, including smoking, a diet high in saturated fat and low in fibre, and a family history of heart disease. ■ Physical disorders and SMI may have a shared genetic propensity. This, along with environmental factors such as an unhealthy lifestyle, may explain the excess physical comorbidity and mortality seen in populations with SMI. ■ People with SMI should be screened for physical comorbidities and provided lifestyle management guidance and general health advice. Metabolic Syndrome The metabolic syndrome describes a cluster of CVD risk factors and metabolic abnormalities including abdominal obesity, hypertriglyceridaemia, low HDL-cholesterol, hypertension and abnormal fasting glucose. It is an important public health syndrome that can be used to identify individuals at increased risk of developing type 2 diabetes and CVD. ► Ethnicity may be a major factor in the development of the metabolic syndrome: 46% of male South-Asian populations living in the UK have the metabolic syndrome, compared to 9% of female Caucasians. ► The metabolic syndrome is especially common in people with SMI. The prevalence of metabolic syndrome has been estimated to be in the range of 30–60% among populations with schizophrenia or bipolar disorder. Individuals with the metabolic syndrome or with one or more components of the metabolic syndrome should receive prompt preventative interventions targeted at individual components of the syndrome. Prevention of the metabolic syndrome is the optimal management strategy, and this can best be achieved through lifestyle interventions such as regular physical exercise and a healthy diet. Issues: 1. Most clinical guidelines agree about the value of regular monitoring of physical health for SMI patients although specific actions are lacking. 2. The risk for metabolic syndrome is: ► Associated with SMI ► Increased by life-style factors (smoking, sedentary lifestyle, obesity, substance abuse, CV risk factors) 3. Most data from clinical trials on metabolic effects of antipsychotics are from retrospective analyses often with treatment biases.	

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		Do guidelines for severe mental illness promote physical health and well-being? Citrome et al J Psychopharmacol 19(6), Supplement (2005) 102–109 The effective management of individuals with severe mental illnesses (SMIs) requires an holistic approach that offers reliable symptom control, but also addresses other clinical, emotional and social needs. The physical health of individuals with an SMI is often poor, with many being overweight or obese, having hypertension, diabetes or dyslipidaemia, and at significant risk of developing cardiovascular disease or other comorbidities. We have recently reviewed current UK and US guidelines for the management of individuals with schizophrenia and bipolar disorder, and found very different approaches to the holistic care of people with SMIs, especially in relation to the management of physical health and cardiovascular risk. UK guidelines acknowledge the high risk of physical morbidity and mortality in individuals with an SMI, but fail to address in detail the specifics of physical health monitoring and lifestyle management. US guidelines are more descriptive in terms of the type and extent of monitoring recommended, but there are inconsistencies between the guidelines produced by different organizations, and studies in the field suggest that none of them is being adequately implemented. Clear and consistent recommendations on how and when to monitor weight, cardiovascular function, and metabolic parameters and, importantly, what to do with the results, would support clinicians wishing to integrate physical and mental healthcare. Publication of specific recommendations on evidence-based physical health interventions that can work for people with SMIs would also help primary care and mental health services improve general well-being in their patients with severe mental illnesses.	

Please add more rows if needed.