Summary

On June 12, 2002, representatives from the Depakote team met with REDACTED in Boca Raton, FL. Abbott attendees included:

REDACTED Development
REDACTED Development
REDACTED, Regulatory Affairs
REDACTED, Development
REDACTED Development
REDACTED Statistics
REDACTED, Depakote Marketing

Questions, regarding Depakote ER in acute mania and schizophrenia, were forwarded to Dr. REDACTED in advance (see Attachment). The discussion focused on the regulatory issues facing Depakote ER for a claim in acute mania and a claim in schizophrenia. For acute mania, Dr. REDACTED concluded that, given the approval for Depakote DR in mania and a prior negative study in acute mania with Depakote ER, at least one positive acute mania trial with Depakote ER must be submitted to the FDA (in the absence of additional negative trials). The discussion regarding a claim in schizophrenia did not lead to any meaningful conclusions. Notable points regarding schizophrenia included a recommendation to re-open discussions with the FDA regarding the path forward and a recommendation to consider utilizing study 010 within a framework of "acute add-on" or "acute adjunctive" treatment of schizophrenia.

REDACTED Comments

Mania

- FDA will agree that Depakote DR is efficacious for acute mania, because they have already approved it for this indication. The question to be answered is whether the new formulation (ER) maintains the efficacy demonstrated by DR.

- Given the prior negative result for Depakote ER, a subsequent negative trial would raise concerns that the ER formulation is not associated with efficacy; at least one more positive trial (in the absence of another negative trial) should be submitted in order to gain approval. In addition, a proportional dosing strategy is unlikely to succeed given the existing negative trial. A subsequent discussion, related to the question of whether one or two additional trials should be conducted, included the possibility that an active control arm could be included in order to provide more persuasive evidence that a trial failed (not that Depakote ER failed). This discussion was more applicable to the scenario in which two trials are conducted and one is positive and one is negative.

- We will not fully understand why the prior Depakote ER in acute mania trial failed; there is no specific or conclusive evidence as to why Depakote failed to separate from placebo. In addition, the reason for efficacy failure in acute mania (as with unipolar

depression) is usually unknown. REDACTED did cite an example of a unipolar depression submission, which was salvaged from apparently failed studies, due to the efforts of a FDA statistician. In addition, some arguments (especially with regard to dose and VPA level in the failed ER study) may undercut arguments for a mania approval if proportionality data is used to support a mania claim.

- Pivotal studies, especially when a single trial is submitted instead of two, must be robust, meaning that a few centers are not carrying the effect and the same effect size is observed no matter how the study population is stratified.

- Internally, FDA reviewers have been trained never to say that a p-value above a threshold doesn't indicate lack of efficacy; instead, the risk/benefit ratio has been shifted.

- "P-values are purchase-able."

- The pediatric mania study may be supportive of the Depakote ER adult mania NDA, but one must consider the likelihood of success of the pediatric mania study.

- REDACTED is relatively more willing to negotiate than REDACTED (due to roles within FDA).

Schizophrenia

- Study 010 is a positive trial (the effect size is robust). Challenges to this interpretation at the FDA probably arise because the discussion is in the context of a new type of claim.

- What to do with the FDA's decision? The FDA may be warning about a future decision—e.g. what are the long-term safety implications? Abbott could re-submit in future with a fully positive trial, but discussion may focus on safety-efficacy balance.

- Much of REDACTED' arguments regarding the difference of this model with epilepsy (ie the adjunctive framework) are somewhat unclear.

- What is it that would justify the use of adjunctive treatment vs. increasing the dose of an anti-psychotic (AP)?

- Due to uncertainty regarding this claim and the FDA's comments, another meeting with the FDA (with REDACTED, REDACTED and REDACTED is warranted. Including REDACTED is even an option. The proposal for a new meeting might include: "we're having difficulty understanding the FDA's recommendation."

- A lengthy discussion on schizophrenia and the potential motivations of FDA personnel started on a more optimistic note and ended more pessimistically. Specifics of the conversation aside, REDACTED stated that he began the conversation with

the belief that Depakote's use in schizophrenia was already well-recognized and study 010 served to reflect existing practice beliefs (similar to the bipolar pivotals for Depakote DR). He ended the conversation with the perspective that study 010 served to create, for the first time, a new use for Depakote (generating excitement in the community, but not necessarily reflecting an existing entrenched practice). The former perspective led REDACTED to cite a 25% likelihood of negotiating a strategy in which a single additional study (for some type of "acute add-on" claim) might be successful, while the latter perspective led REDACTED to cite a 10% likelihood of success.

- Comments under the earlier perspective (that Depakote in schizophrenia, as demonstrated by study 010, is already established practice) included:
  - Build buy-in from opinion leaders in support of new discussions with FDA (REDACTED).
  - The arguments provided by REDACTED are not consistent with his logic historically.
  - The division, however, "jealously guards the protocol-specified primary."
  - Definitions of onset have been historically problematic (REDACTED has never liked the definitions of onset as recommended by REDACTED, REDACTED et al).
  - While we have agreed with the FDA that study 010 does not support combination use (as defined strictly the combination being superior to each agent alone), we could still argue for study 010's applicability to add-on (including the idea that, although patients may have undergone a pharmacokinetic washout, there was not an effective pharamacodynamic washout and Study 010, therefore, was an add-on study).
  - One option is to repeat study 010, conduct it anyway we wish (including AUC endpoints, no washout) and submit an NDA for "acute add-on." If the NDA is not accepted, go up the FDA ladder. This proposal should be adequate for efficacy, but safety (especially safety-efficacy balance) will be the contentious issue.
  - An inside-FDA political issue may relate to the dynamics between REDACTED and REDACTED. In this case, REDACTED may be deferring to REDACTED, who may not be flexible.

- REDACTED had raised several questions regarding how Depakote should be used in schizophrenia (when would one choose to increase the dose of an atypical vs. adding Depakote, which patient types, which atypicals, what is the definition of being maximized on an atypical, etc), none of which could be adequately answered at this time.

- Durability of treatment could be addressed with discontinuation designs (randomized withdrawal of responders).

- An "adjunctive" claim begs the question of what kinds of patients should be treated with Depakote and where in the course of their treatment should they receive Depakote?

- Strictly speaking, "combination" refers to fixed combination studies (21CFR300.5), and is a concept being stretched to fit the current proposal. In this situation, one's

goal is only to show that Depakote alone is not active. With respect to the inclusion of a placebo arm, placebo should be non-controversial in a study of non-responders (if a combination or add-on study were to include such patients).

Minutes written by REDACTED June 25, 2002.

Attachment

Questions: Bipolar Program

1. What is the smallest package of data to obtain an approval of Depakote ER in mania? What is the likelihood of success?
2. Given that the M97-696 study of Depakote ER in the treatment of mania was a negative trial, would one additional adequate and well-controlled study be sufficient for obtaining an indication label for ER in the treatment of mania? Estimate the probability of success, in obtaining a label for ER in the treatment of mania, with one more study. Given rates of failed trials in psychiatry would you recommend doing 1 or 2 trials in mania?
3. Given the results of M97-696, does the newly proposed study, M01-346, address the potential shortcomings of the original trial design and adequately control for potential placebo response? Are there any other design features that could be added to the current proposed trial to enhance recruitment and minimize a placebo response?
4. Could the indication for Depakote ER in bipolar be obtained with a PK argument?
5. Will a positive pediatric study with Depakote ER (as proposed in the PPSR) provide support of a label in mania?

Questions: Schizophrenia Program

1. What is the smallest package of data needed to obtain an indication of adjunctive Depakote ER in the treatment of schizophrenia?
2. Under what circumstances would one trial be adequate for approval?
3. Which treatment paradigm would be a more successful strategy in pursuing an indication:
   - a combination approach (simultaneous initiation of Depakote with an antipsychotic agent in patients in an acute exacerbation of schizophrenia)
   - add-on approach (Depakote added on to an existing antipsychotic agent in partially responding patients), or
   - one combination trial and one add-on trial?
4. If two trials are required for a combination indication, must a Depakote/placebo group be required for both trials?
5. Given what the FDA has already stated in the minutes of the March 4, 2002 meeting, do you think that the agency would require a study with a placebo/placebo group?
6. Do you think that approval in this indication would be accompanied by a phase IV commitment (e.g., pediatric, safety, maintenance)?
7. Do you think the agency will require PK data? If so, what might they require?