Version Date: May 9, 2002

# AGENCY NEGOTIATION WORKSHEET - INSTRUCTIONS

**How to use this tool:**

1. Refer to the Regulatory Plan and overall team development strategy.
2. List the key issues that will be negotiated with the agency during this interaction.
3. Review the key issues with your Director and any technical mentors you feel would add value to this effort.
4. Discuss the issues with the team, identify any other issues, and determine the company's strategic positions on each ("**NEED", "WANT",** & **"STRETCH"**).

   **STRETCH: Low probability of regulatory success; High leverage potential for current compound or future development projects; Would accelerate current timeline**

   **WANT: Desired outcome from meeting, Medium probability of regulatory success, Often serves as the basis of the briefing document; Keeps development timeline on track to current plan**

   **NEED: Absolutely need from the meeting; High probability of regulatory success; Well grounded in regulatory reality**

   **UNDESIRABLE/NEGATIVE OUTCOME: Adversely affects strategy or timeline**

5. Complete the Worksheet. For Section II, this may require some additional prework using the method of your choice. This prework will facilitate the focusing of issues for the Briefing Document.
6. Develop the Briefing Document for submission to agency to resolve key issues. Gain agreement with team on how questions should be ordered (most critical first, or most logical order for desired outcome)
7. Schedule time with Ann Gibson (7-1949) to make presentation to the "WIN" Council (should be at least two weeks prior to the Briefing Document being submitted)
8. Distribute completed worksheets at least 24 hours in advance of "WIN" Council meeting to members, G. Brophy, T. Copmann, G. Enas, P. Gesellchen, E. Sloan, J. Stotka, T. Massa, and L. Holzhausen with cc to their AA's.
9. At least two (2) weeks prior to the submission of the Briefing Document, have a meeting with the WIN council to review Section II.. They will serve as a discussion/comment forum for Section II.
10. Finish preparation of the Briefing Document.

**11.** Following the Agency meeting, assess the outcome for each issue by completing the Section I (Summary Section) table. Mark an "X" in the Outcome column that reflects the outcome for each issue discussed in the Agency interaction.

# AGENCY NEGOTIATION WORKSHEET

## I. SUMMARY SECTION

Product/Division: Zyprexa – Discussion of Glucose/ CDER-Neuropharm Meeting Date: October 17, 2002, 2002

Type of Meeting: Discussion of safety data Regulatory Scientist/Associate: M. Bruno Council
Date: September 25, 2002 Version 1

| ISSUES and OBJECTIVES (WHAT'S AT STAKE)<br>Refer to Regulatory Plan and Strategy Document | | | | | |
|---|---|---|---|---|---|
| **STRATEGIC ISSUES TO BE NEGOTIATED**<br>One issue per line; list in order of importance. Expand table as needed to accommodate additional issues. | **WHAT IS AT STAKE?**<br>What element(s) of the regulatory strategy is dependant upon resolution of this issue? Why this issue is important to the regulatory strategy; *e.g.*, label claim, development time, L30S, etc. | **OUTCOME**<br>(mark result with "X" in correct | | | |
| | | **STRETCH GOAL** | **WANT** | **NEED** | **N** |
| **1.** Gain understanding of the Division's position regarding Lilly's interpretation of data presented in the briefing document including: study HGIM, study S013, retrospective analysis on TED, Glucose 4 (Postmarketing-Clintrace), MedWatch FOI, Advanced PCS database and the GPRD database analysis within the context of the evolving information in the field. | Future labeling for Zyprexa and potentially other antipsychotics regarding glucose dysregulation. | | | | |
| **2.** Gain understanding regarding what data FDA is examining pertaining to glucose dysregulation, if there are any new data expected soon, and whether Lilly's data are demonstrating the same outcomes as FDA's. | Future labeling for Zyprexa and potentially other antipsychotics regarding glucose dysregulation. | | | | |
| 3. Gain FDA perspective on a proposed study design that would address the impact of therapy on glycemic events. | Decision to move forward with a new trial. | | | | |

**BRIEF DESCRIPTION OF MEETING:**

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**NEW OR UNRESOLVED ISSUES IDENTIFIED AT MEETING:**

# II. PLANNING SECTION

| ISSUE 1: Gain understanding of the Division's position regarding Lilly's interpretation of data presented in the briefing docume HGIM, study S013, retrospective analysis on TED, Glucose 4 (Postmarketing-Clintrace), MedWatch FOI, Advanced PCS databa database analysis within the context of the evolving information in the field. | | |
|---|---|---|
| **COMPANY NEED**<br>Absolute need from the meeting,<br>Well grounded in Regulatory Reality<br>High Probability of Success | **COMPANY WANT**<br>Desired outcome from meeting –keep development timeline on track to current plan<br>Regulatory Probability of Success=Medium | **COMPANY STRETCH GO**<br>High leverage potential if suc current timeline<br>Regulatory Probability of Su |
| FDA's opinion on Lilly's interpretation of the data and the conclusions (cumulative data currently available do not indicate consistent, substantial differences in the risk for diabetes of in changes in markers of glucose). | FDA's agreement with Lilly's conclusions that is: cumulative data currently available do not indicate consistent, substantial differences in the risk for diabetes of in changes in markers of glucose. regulation in patients treated with olanzapine compared with other atypical antipsychotics. | FDA believes that no additio come to conclusions regardir dysregulation in atypical anti there is no anticipation of lab |

**LILLY POSITION (Explain Lilly position/caveats on issue)**

**Background**

Historically, the scientific literature has supported the concept that there is a higher prevalence of diabetes in patients with schiz several years, Lilly has been conducting a number of olanzapine studies that have obtained information with respect to paramete regulation. In 2000, FDA asked Lilly to provide an update of this information to the Agency. This available information was pr

In terms of information now available to FDA, Lilly has conducted two clamp studies (HGIM and S013) that address the issue o secretion and sensitivity. These studies (conducted in healthy volunteers) showed that olanzapine and risperidone do not have a insulin secretion or insulin sensitivity. In addition, Lilly has performed a retrospective analysis of the Lilly clinical trial databas treatment emergent diabetes (TED). This TED study indicated that patients that develop diabetes represent a subgroup with a hi known risks for diabetes or have evidence suggestive of pre-existing unrecognized glycemic abnormalities. Lilly's analysis of a from Lilly's postmarketing database (first five and one-half years of commercial marketing of olanzapine through 31 March 200 summarized in Glucose 4. The conclusion from Glucose 4 is that an overwhelming majority of spontaneous adverse events asce glucose dysregulation were confounded by the presence of baseline risk factors for diabetes, medical conditions which have bee glucose homeostasis or concomitant treatment with drugs known be associated with glucose dysregulation. Similarily, the FDA database has been examined for reports received though September 2001. Differences were observed among the reporting rates olanzapine, quetiapine, risperidone and ziprasidone, however due to the nature of these data (bias, lack of population control), in causality can not be ascertained. The previously submitted (2000) cohort studies have not demonstrated consistent substantial di likelihood of concomitant diabetes or new diagnoses of diabetes among patients receiving different atypical antipsychotic medic

Based on these data, Lilly's overall conclusion is: cumulative data currently available do not indicate consistent, substantial diff diabetes of in changes in markers of glucose for olanzapine compared with other atypical antipsychotics.

**Lilly Position**

The examination of the data available to Lilly has led to a reasonable scientific conclusion. The potential limitations of the HGI that these studies were performed in healthy volunteers and while there is scientific reasoning to support the choice of a healthy studies, the Agency may prefer to have the data in the psychiatric patient populations. This could result in the Agency asking fo studies in patients with schizophrenia and bipolar disease if the Agency feels that the results are not generalizable to the schizop populations. While postmarketing databases are useful to identify potential signals that should be examined, there are limitation factors or lack of essential information in a lot of the cases (e.g. information on weight gain, risk factors for diabetes). These lim the usefulness of the data for conclusions as to causality. Lilly is proposing a potential prospective trial design that could potent glycemic control. Overall, the goal of the first issue is to gain the Division's perspective on where they are data-wise and interp issue of glucose dysregulation. FDA may share their thoughts regarding future labeling for atypical antipsychotics.

**AGENCY POSTION (Explain Agency position/caveats on issue)**

The Agency is likely to provide an opinion that they are in agreement with the individual conclusions of each dataset, but may n overall conclusion. The Agency may have or may be obtaining additional data (the "VA" study) that could provide additional in FDA to reach a different conclusion. It is expected that the Division with be appreciative of Lilly's sharing of the most recent da combination with any proprietary or incoming information will allow FDA to have a more complete picture of the role, if any, o antipsychotics in glucose dyregulation in the schizophrenia/bipolar populations. The Division has some awareness that the schiz has a disease factor which results in the population having a higher incidence of glucose dysregulation and diabetes and this coul point of view regarding data. Lack of agreement to the conclusions in reference to HGIM and S013 data would primarily be due healthy volunteers in the studies, small N and control conditions.

**ISSUE 2:** Gain understanding regarding what data FDA is examining pertaining to glucose dysregulation, if there are any new and whether Lilly's data are demonstrating the same outcomes as FDA's.

| **COMPANY NEED** | **COMPANY WANT** | **COMPANY STRETCH GO** |
|---|---|---|
| Absolute need from the meeting,<br>Well grounded in Regulatory Reality<br>High Probability of Success | Desired outcome from meeting –keep development timeline on track to current plan<br>Regulatory Probability of Success=Medium | High leverage potential if suc current timeline<br>Regulatory Probability of Su |

| | | |
|---|---|---|
| The company needs to know what additional data could be considered as helpful in FDA's evaluation of glucose dysregulation and when new information (the "VA" study) is anticipated to be finished and data interpreted. From this information the company can project when FDA may be likely to update atypical antipsychotic labeling. | The company would like to learn about the outcome of the VA study (if available) and whether the cumulative data that Lilly's has examined is consistent with the interpretation/trends seen in data available to FDA. | The company would like to k<br>what the Division's final opi<br>be regarding glucose dysregu<br>antipsychotics.<br><br>In terms of labeling: FDA ag<br>labeling with emphasis on ps<br>and risk factors. |

**LILLY POSITION (Explain Lilly position/caveats on issue)**

**Background**

From conversations with FDA, it has become apparent that there is an ongoing "VA" study about which little is know in terms o completion and timing of data analysis. It has been speculated that this "VA" study is a retrospective analysis of the large VA d Agency would be exploring the emergence of glycemic events for patients on atypical antipsychotics. These data could provide other data available to FDA to modify labeling for atypical antipsychotics.

**Lilly Position**

Lilly has performed exhaustive, multimodal analyses on a variety of data regarding glucose dysregulation with atypical antipsyc information in Issue 1) based on the information available to Lilly. Since Lilly is aware of the "VA" study and this presents a w information regarding atypical antipsychotics, it would be most important to know what the parameters of the study are and ulti interpretation. Since these data are likely to profoundly influence the Division's opinions on glycemic control in atypical antips that the design is not flawed and that interpretations of these data are scientifically sound and medically appropriate. It is also in know whether these data are trending in the same manner as the data Lilly has examined regarding glucose dysregulation.

**AGENCY POSTION (Explain Agency position/caveats on issue)**

It is expected that the VA study will not yet be complete (perhaps near completion) by the time of the October 17, 2002 meeting having their preparation meeting for the October 17th meeting on October 16th. The Agency is likely to share the parameters of t not be able to respond regarding their conclusions based on the study data. They should be able to state how influential these da Lilly know when these data would be available. In addition, the Division may provide information regarding any anticipated lab to these data.

| **ISSUE 3:** Gain FDA perspective on a proposed study design that would address the impact of therapy on glycemic events. | | |
|---|---|---|
| **COMPANY NEED**<br>Absolute need from the meeting,<br>Well grounded in Regulatory Reality<br>High Probability of Success | **COMPANY WANT**<br>Desired outcome from meeting –keep development timeline on track to current plan<br>Regulatory Probability of Success=Medium | **COMPANY STRETCH GO**<br>High leverage potential if suc<br>current timeline<br>Regulatory Probability of Su |
| The Division's agreement to something close to the current study design parameters (i.e. open label vs blinded) so that a study could be completed within a reasonable period of time. | The Division's agreement that there is no need for further studies as the results would not be timely for labeling purposes. | If a study is initiated, no acti<br>antipsychotic labeling until a<br>complete. |

**LILLY POSITION (Explain Lilly position/caveats on issue)**

**Background**

Lilly is proposing a study design, which would evaluate potential effect of therapy with olanzapine versus a comparator for the e glycemic events. The proposed design would be a randomized, open-label, parallel, comparator-controlled, 1-year study to comp new glycemic events during treatment with olanzapine versus an atypical antipsychotic comparator. This study would also asses of preexisting diabetes risk factors (eg, baseline glucose, body mass index, age, ethnicity, lipid profile, hypertension, family hist activity), weight gain, and atypical antipsychotic therapy on incidence of new glycemic events. As secondary objectives, this pr assess baseline to endpoint changes in glucose, insulin, and lipids; examine the relationship of weight gain to mean change in lab explore the relationship between indicators of acute and chronic illness severity and metabolic endpoints.

**Lilly Position**

Lilly thinks that this study presents a number of implementation challenges and would pursue this avenue if FDA feels that this t fill an important data gap. Lilly is interested in hearing alternative suggestions from the Division.

**AGENCY POSTION (Explain Agency position/caveats on issue)**

The Division will likely look favorably on this type of study proposal that could address potential data gaps. It is expected that t comments on the study design or that they may suggest alternative or additional investigations.

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# WIN METRIC SCORE SUMMARY

| | |
|---|---|
| **WIN** Outcome that keeps strategy or timeline on track, or improves it in some way **[Stretch Goal and Want]** | **No. of X's** |
| **NEUTRAL** (Outcome that is minimally acceptable; may not adversely affect strategy/timeline *per se*, but may require additional effort or contacts with Agency to resolve) **[Need]** | |
| **LOSS** (Undesired/Unexpected Negative Outcome; adversely affects strategy or timeline) **[Undesireable/Negative]** | |

| PROJECTS | DATES | ISSUES | STRATEGY | OUTCOME | | |
|---|---|---|---|---|---|---|
| | | | | STRETCH GOAL | WANT | NEED |
| | | | | | | |
| | | | | | | |
| | | | | | | |

**UNEXPECTED OUTCOMES (Positive or Negative) :**