

[initials]

# October 17, 2002 Glucose Dysregulation FDA Meeting Meeting Preparation Document

**Meeting Logistics:**

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For those that need lodging- stay at Doubletree Hotel in Rockville Maryland

Meet at Rockville Office (connected to the Double Tree, Floor 4) at 9:00am on October 17<sup>th</sup>.

Leave for FDA on shuttle bus at 10:40am. Please bring ID.

Have meeting.

Leave FDA, go to Airport for 1:15pm flight back to INDY. Debrief meeting on the plane. Alan to call management and leave message for Zyprexa Team, Melanie to call Regulatory Management, Laura to call Symbiax Team.

Leave Washington D.C.

**Meeting Attendees:**

**FDA:** Russell Katz, M.D. (Division Director), Thomas Laughren, M.D. (Medical Team Leader), Judy Racoosin, M.D. (Safety Physician), Jerry Boem (safety physician reports to Judy Racoosin) Steve Hardemans, (R.Ph., Project Manager) *Paul arduosyn - Zyprexa reviewed*

**Lilly:** Alan Breier, M.D. (VP, Research Fellow & Zyprexa Team Leader) Gregory Brophy, Ph.D. (Director, US Regulatory Affairs), Melanie Bruno, Ph.D., MBA. (Senior Regulatory Research Scientist), Patrizia Cavazzoni, M.D. (Clinical Research Physician, Safety Subteam Leader), Missy Sowell, M.D. (Clinical Research Physician, Endocrinologist), Laura Fludzinski (Symbiax Team Leader)

**Consultants:** John Buse, M.D. (Univeristy of North Carolina)

**FDA Premeeting:**

FDA will have its premeeting on October 15th at 9am. Melanie will call Steve Hardeman for feedback about 12:00 Indy time..

**Proposed Conference Table Seating:** Starting at the overhead: Melanie, Alan, Patrizia, John, Missy, Greg. Laura -wall seat with best view.

**Proposed Meeting Agenda:**

Introductions (usually initiated by Dr. Katz), Thanks for having us in today, explain flow of meeting-no presentation, lets get right to questions (Alan or Melanie), go to questions (Melanie to put question up on overhead/record answer on overhead/verify understandings), discussion of questions (ALL- Alan to lead).

**New Information:**

The "VA" study appears to have been initiated by the PBM of the VA not FDA. Apparently, FDA has asked to look at the data. According to consultants, after the study is completed (range 4 to 6 months or later), the information will be shared with FDA and then with the pharma companies. The study is looking at glucose related issues including Hemoglobin A1C, as well as lipids and triglycerides.

**Other questions we need answered that aren't explicitly stated in briefing document:**

Need to understand where FDA may be going with labeling and by when.

Redacted

## Question 1: Clamp studies

### Potential FDA questions:

#### **What about the within group change for olanzapine?**

- -Primary is primary and the most appropriate and sensitive measure (clamp)
- Absolute change at endpoint is comparable to risperidone baseline, with group data stats within normal variance
- Within group change in fasting glucose and fasting insulin are not a reliable estimate except in large epidemiological studies
- Negate relevance of secondaries: Physiological mechanisms that could be relevant to secondaries: changing diet (level of protein), activity level (olanzapine more sedate), motility of bowel, lack of multiple collections (pulsatile nature of hormone release).

#### **What about a larger sample size?**

- For other drugs, clamp studies have shown an effect on glucose in studies with similar duration and sample size
- Could do another study, but why?

#### **Why weren't patients used in the clamp studies? Why are the results in healthy normals generalizable to population?**

- -state why it is appropriate to use patients-this is outlined in Briefing Document (Missy working this)
- Newcomer data supports the same results in schizophrenic patients

#### **How to reconcile data with Henderson study?**

- Do another study

### Overall points:

1. Clamp measure are identifying insulin effects across drug/disease state in studies of similar duration and sample size
2. Newcomer data supports the same results in schizophrenic patients
3. Zyprexa does not effect insulin secretion or sensitivity

## Potential FDA Label Strategy/Questions:

### Overall Strategy:

- **Want to learn status of thinking regarding glucose?**
- **Is there an imminent label change, if so what, procedural how (submissions, FDA Advisory Committee (joint with endocrine or possibly Symbiax) and by when?**
- **Is there no anticipated label change?**

**Do you (Lilly) think Zyprexa is appropriately labeled? YES, no label change**

- We want to get it right
- Digesting new data (TED, Clamp, FOI, Spontaneous)
- Don't see conclusive scientific evidence (causal) since the data are confounded.
- We recognize that there is a lot of current attention in media/competitors
- Incidence of diabetes in the Schizophrenia population is greater than the general population-disease course
- Do have AE labeling
- Educational initiatives could be helpful in increasing awareness of diabetes in the population with psychiatric illness.

**Are you going to change your label in the US since the labeling has been changed in Japan, Australia, New Zealand and potentially Canada and there is already more information in the EU label than the US label?**

- The labeling changes in Japan and other countries has not been based full scientific consideration of the available data, but rather forced upon Zyprexa.

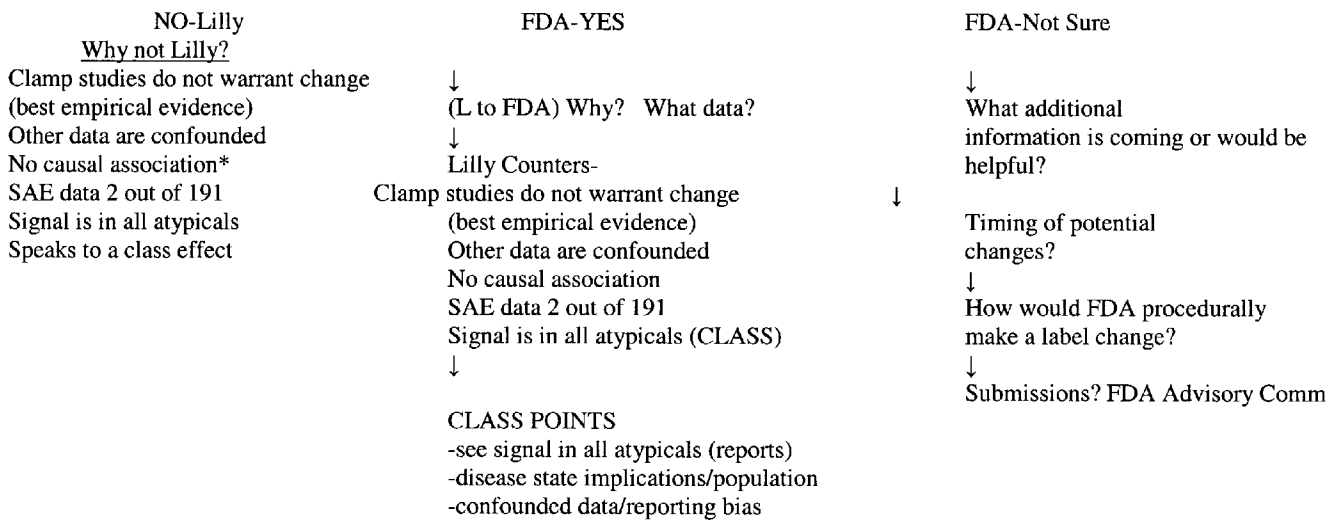
**Even if the FOI and postmarketing databases are known to be flawed methodologically, it seems that olanzapine is in the lead number-wise as compared to other atypical antipsychotics, so why shouldn't olanzapine have differential labeling?**

- All the antipsychotics are showing a signal and since the data are confounded it is to the benefit of the prescribers (so that they can provide the best care) and to the patients to have the information in all the labels since this seems to be a class effect.

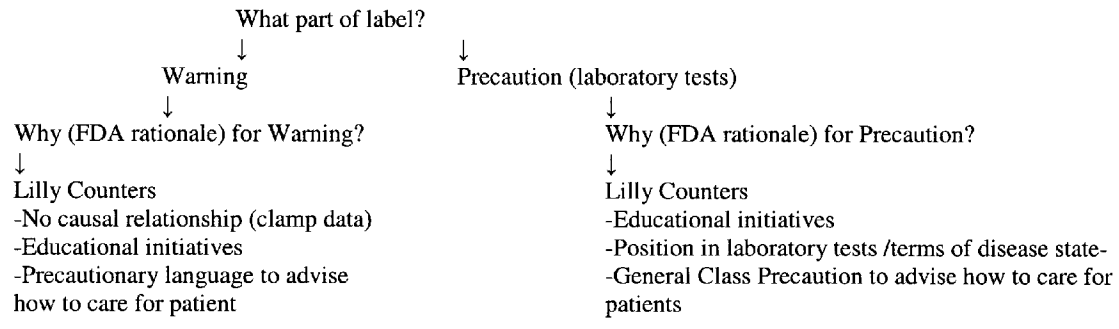
**To John Buse: Do you think there needs to be a labeling change for Zyprexa in terms of hyperglycemia/diabetes? If so, what kind of change? Should this be a class label change for all antipsychotics?**

Should we change our label?

We keep on looking at our data and at the new data as it comes in and ask the question and we want to get it right-data driven.



\*Warnings can be implemented without Causality



**WHAT IF: BOLDED WARNING –usually based on clinical data**

- Not warranted by the data
- Lack of causality and clinical data (well controlled) does not support
- What kind of studies to alleviate concern?
- Be willing to do a another clamp in patients
- Could explore rechallenge study
- Timing-would ask to wait until full consideration of appropriate data
- Offer a precaution until the work can be done
- Offer to do education

**WHAT WOULD MAKE LILLY CHANGE THE LABEL?**

- A signal in a scientifically rigorous clamp study
- If there were nonconfounded cases in the literature

**Question 2: Comparative risk within class-agree with overall interpretation?**

Potential FDA answers Yes/No

Yes-then ok for LillyNo-

- Lilly to ask why FDA does not agree and on what points.
- FDA could ask : Why have you reached conclusion X for X?

**Question 3: Olanzapine in context of overall data? Are Lilly data/conclusions in line with FDAs?**

Potential FDA answers Yes/No

Yes-then ok for LillyNo

- Lilly to ask why and understand FDA positions, provide clarity to misunderstandings regarding data

**Question 4: Any additional data?**

Potential FDA answers Yes/No

Yes

- What are those data?
- When is the data anticipated?
- When would this be shared with Lilly if it would impact Lilly labeling?

No- Lilly ok so long as with lack of new data there is no labeling change.

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### **Question 5: Data Gaps?**

Potential FDA answers –Yes/No

Yes

- What are those gaps?
- FDA could also ask Lilly what we think the gaps are-what are they?
  
- How to best address these gaps?
- Will Division wait for new data to make any labeling change decisions-even if it takes a while so that the labeling is data driven?

No- Lilly ok so long as with lack of new data there is no labeling change.

### **Question 6: Educational initiatives-asking comment on their perspective on initiatives**

Potential FDA answers:

- Valuable
- Do more
- More effective than labeling
- Not valuable
- A marketing ploy

John Bose thinks that re challenge studies should be done  
to improve drug studies which were too small to rule out  
effect.

John Bose has seen ~20 cases of DKA that just appeared w/o patient  
having been identified as diabetic I or II type.

Concerned about good drug / bad drug perception of prescribers +  
patients if drugs are labeled individually + differently

John Bose -

class labeling if any labeling  
risk factors can be identified  
patients can be counseled

concern - counter detailing is going on despite data - causing confusion

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