To:	CN=Charles M Beasley Jr/OU=AM/O=LLY@Lilly; CN=Paul Berg/OU=AM/O=LLY@Lilly; CN=Mark J Bernauer/OU=AM/O=LLY@Lilly; CN=Julie Birt/OU=AM/O=LLY@Lilly; CN=William P Brookfield/OU=AM/O=LLY@Lilly; CN=Anthony M Fiola/OU=AM/O=LLY@Lilly; CN=Kristine Healey/OU=AM/O=LLY@Lilly; CN=Kenneth Hornbuckle/OU=AM/O=LLY@Lilly; CN=Jared G Kerr/OU=AM/O=LLY@Lilly; CN=Kenneth C Kwong/OU=AM/O=LLY@Lilly; CN=Mark D Millikan/OU=AM/O=LLY@Lilly; CN=Jeffrey T Ramsey/OU=AM/O=LLY@Lilly; CN=H John Roth/OU=AM/O=LLY@Lilly; CN=Michele Sharp/OU=AM/O=LLY@Lilly
CC:	CN=Starr Grundy/OU=AM/O=LLY@Lilly; CN=Anna Thornton/OU=AM/O=LLY@Lilly
Date:	06/04/2001 02:30:29 PM
From:	CN=Anna Thornton/OU=AM/O=LLY
Subject:	Summary from FDA symposium: Evaluating a Safety Signal in the Postmarketing Period: Hyperglycemia and the Atypical Antipsychotic Drugs

FYI (please delete if you have already received!) --

Information regarding a presentation made at NCDEU last Thursday.

Thanks Starr for the summary!!

Anna
(x77076)

Bryan Johnstone

05/31/2001 05:53 PM

To:	Alan Breier/AM/LLY@Lilly, Robert A Browne/AM/LLY@Lilly, Suzanne F Clifford/AM/LLY@Lilly, James B Gregory/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Marni Lemons/AM/LLY@Lilly, John R Richards/AM/LLY@Lilly, Virginia Stauffer/AM/LLY@Lilly, Robert K Thompson/AM/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Vincent P Truax III/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly, US_NS_MD, Jill R Welch/AM/LLY@Lilly, Dennis G West/AM/LLY@Lilly, Frederic Wieler/AM/LLY@Lilly
cc:	Starr Grundy/AM/LLY@Lilly
Subject:	Summary from FDA symposium: Evaluating a Safety Signal in the Postmarketing Period: Hyperglycemia and the Atypical Antipsychotic Drugs

Fyi,

Summary of today's FDA presentation at the NCDEU meeting on the atypical antipsychotics and hyperglycemia. Thanks to Starr Grundy for providing this information.

Bryan
----- Forwarded by Bryan Johnstone/AM/LLY on 05/31/01 04:50 PM -----

Starr Grundy

05/31/01 04:37 PM

To: US_Neuro_ML
cc: Robert W Baker@Lilly, Patrizia Cavazzoni@Lilly
Subject: Summary from FDA symposium: Evaluating a Safety Signal in the Postmarketing Period: Hyperglycemia and the Atypical Antipsychotic Drugs

Dear All,

I have typed up the notes that I took this morning from this symposium. If you attended, please feel free to add additional comments that I have missed.

Best regards,
Starr

Thursday, May 31, 2001
10:00-10:30
Evaluating a Safety Signal in the Postmarketing Period: Hyperglycemia and the Atypical Antipsychotic Drugs
Judith Racoosin, M.D., MPH; FDA

Steps in evaluation process
-identification of safety concern
-evaluation
-collection of additional data
-further epidemiological study
-risk-management options

How are safety concerns identified?
-case reports
-adverse events reported through Medwatch
-sponor identifies issue when reviewing reported adverse events

Examples of Case Reports that have been further evaluated by the FDA:
1. Clozapine and Myocarditis
2. SSRI's and GI bleeding
3. Atypical Antipsychotics and reports of hyperglycemia, diabetes mellitus

Review of Reports to the Adverse Event reporting system
-Safety evaluators focues on serious, unlabeled events
-When a serious of concerning reports accumulates, the safety evaluators compiles a case series.

Calculation of Reporting Rates
-Usage data is obtained
-OPDRA contracts with IMS
-National Disease & Therapeutics Index provides statistical information on the patterns of the treatments of diseases
-person years = # prescriptions/12 (assumes one prescription = 30 days)
-reporting rate = # of cases/person years

Caveats for Interpreting Reporting Rates
-reporting rate does not equal incidence rate due to a substantial amount of underreporting (numerator) and potential inaccuracy of exposure estimate (denominator)
-reporting is not consistent from year to year or from event to event
-duration product is on the market (greatest in first 3 years post launch)
-serious or unexpected events are reported until they become part of the clinical culture
(e.g., rash with lamotrigine)
-need to consider increase in overall frequency of reporting (cannot compare old reporting with the "typical" antipsychotics with current reporting with the "atypical" antipsychotics.

Reporting Rates
-compare reporting rate to the background rate of the event in the population
-done by looking at epidemiological studies, literature, vital statistics, National Hospital Discharge survey
-concern arises if it meets or exceeds background rate (especially because of the problem of underreporting).

Factors to consider when reviewing cases
-background incidence in population (disease; e.g., diabetes in schizophrenia being reported before the introduction of antipsychotics)
-are risk factors known
-can the condition be asymptomatic and then discovered at a change of treatment

Reporting Rates 1999

	Clozapine	Risperidone	Olanzapine	Quetiapine
Year marketed	1991	1994	1996	1997
Total US patients	11.4	14.9	8	1.1
Reporting period	1/93-9/99	1/94-6/99	1/96-8/99	1/97-1/99
	n/Rate	n/Rate	n/Rate	n/Rate
New-onset DM (NODM)	90/18	55/4.5	81/12	1/1.1
NODM, with DKA	27/5.4	10/0.8	37/5.6	1/1.1
NODM, with NHHS	6/1.2	4/0.3	5/0.5	0/0.0

Dr. Racoosin mentioned that there appeared to be a difference in the rate reported with clozapine and olanzapine in this sample compared with risperidone and quetiapine.

Once a safety signal is generated, it can be useful to return to the NDA
-similar adverse events?

She reviewed the data collected from Study 054
-noted that there was a difference between olanzapine and others
-however, she did note that there didn't appear to be a difference for Outliers in any of the treatment groups for fasting glucose and insulin(from Study 054).

Further Epidemiological Study
-study of adverse events is not usually ammenable to a randomized double-blind, controlled trial.
-two options for observational studies
    -Sponsor Supported
    -FDA cooperative agreements
        -OPDRA administers an extramural research program that addresses regulatory safety questions

Risk Management Options
-labelling changes
    -ranges from inclusion in "post-introduction section" to addition of "Black Box"
-Patient package insert
-Medication guidance
-Restricted distribution
-Withdrawal

During the Q & A session someone in the audience asked the question: Where is the FDA headed with atypicals and diabetes?

The FDA is in the process of gathering additional data:

- Have already
  - Spontaneous report review
  - NDA review
  - Sponsor epidemiologic submissions
- Considering starting their own trials
  - -possibly adding onto the CATIE trials in schizophrenia
    - -glucose
    - -glycosylated hemoglobin

Currently, only clozapine has language in its labelling and they are discussing other products; no decisions have been made.